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(54) Title: RENAL-SELECTIVE PRODRUGS FOR CONTROL OF RENAL SYMPATHETIC NERVE ACTIVITY IN THE TREATMENT OF HYPERTENSION

(57) Abstract

Renal-selective prodrugs are described which are preferentially converted in the kidney to compounds capable of inhibiting synthesis of catecholamine-type neurotransmitters involved in renal sympathetic nerve activity. The prodrugs described herein are derived from inhibitor compounds capable of inhibiting one or more of the enzymes involved in catecholamine synthesis, such compounds being classifiable as tyrosine hydroxylase inhibitors, or as dopa-decarboxylase inhibitors, or as dopamine-β-hydroxylase inhibitors. These inhibitor compounds are linked to a chemical moiety, such as a glutamic acid derivative, by a cleavable bond which is recognized selectively by enzymes located predominantly in the kydney. The liberated inhibitor compound is then available in the kidney to inhibit one or more of the enzymes involved in catecholamine synthesis. Inhibition of renal catecholamine synthesis can suppress heightened renal nerve activity associated with sodium-retention related disorders such as hypertension. Conjugates of particular interest are glutamyl derivatives of dopamine-β-hydroxylase-inhibitors, of which N-acetyl-γglutamyl fusaric acid hydrazide [represented in formula (a)] is preferred.



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RENAL-SELECTIVE PRODRUGS FOR CONTROL OF RENAL SYMPATHETIC NERVE ACTIVITY IN THE TREATMENT OF HYPERTENSION

Related Application

This application is a continuation-in-part of U.S. Application Ser. No. PCT/US90/04168 filed 25 July 1990, which is a continuation-in-part of U.S. Application Ser. No. 07/386,527 filed 27 July 1989.

Field of the Invention

This invention is in the field of cardiovascular therapeutics and relates to a class of compounds useful in control of hypertension. Of particular interest is a class of compounds which prevent or control hypertension by selective action on the renal sympathetic nervous system.

20 Background of the Invention

Hypertension has been linked to increased sympathetic nervous system activity stimulated through any of four mechanisms, namely (1) by increased vascular resistance, (2) by increased cardiac rate, stroke volume and output, (3) by vascular muscle defects or (4) by sodium retention and renin release [J. P. Koepke et al, The Kidney in Hypertension, B. M. Brenner and J. H. Laragh (Editors), Vol. 1, p. 53 (1987)]. As to this fourth mechanism in particular, stimulation of the renal sympathetic nervous system can affect renal function and maintenance of homeostasis. For example, an increase in efferent renal sympathetic nerve activity may cause increased renal vascular resistance, renin release and sodium retention [A. Zanchetti et al, Handbook of Hypertension, Vol. 8, Ch. 8,

vasoconstriction has been identified as an element in the pathogenesis of early essential hypertension in man. [R. E. Katho:, Amer. J. Physiol., 245, Fl-F14 (1983)].

Proper renal function is essential to 5 maintenance of homeostasis so as to avoid hypertensive conditions. Excretion of sodium is key to maintaining extracellular fluid volume, blood volume and ultimately the effects of these volumes on arterial pressure. Under steady-state conditions, arterial pressure rises to that pressure level which will cause balance between urinary output and water/salt intake. If a perturbation in normal kidney function occurs causing renal sodium and water retention, as with sympathetic stimulation of the kidneys, arterial pressure will increase to a level to maintain 15 sodium output equal to intake. In hypertensive patients, the balance between sodium intake and output is achieved at the expense of an elevated arterial pressure.

During the early stages of genetically 20 spontaneous or deoxycorticosterone acetate-sodium chloride (DOCA-NaCl) induced hypertension in rats, a positive sodium balance has been observed to precede hypertension. Also, surgical sympathectomy of the kidneys has been shown to reverse the positive sodium balance and delay the onset of 25 hypertension [R. E. Katholi, Amer. J. Physiol., 245, F1-F14 (1983)]. Other chronic sodium retaining disorders are linked to heightened sympathetic nervous system stimulation of the kidneys. Congestive heart failure, cirrhosis and nephrosis are characterized by abnormal chronic sodium 30 retention leading to edema and ascites. These studies support the concept that renal selective pharmacological inhibition of heightened sympathetic nervous system activity to the kidneys may be an effective therapeutic treatment for chronic sodium-retaining disorders, such as 35

hypertension, congestive heart failure, cirrhosis, and nephrosis.

One approach to reduce sympathetic nervous system effects on renal function is to inhibit the synthesis of one or more compounds involved as intermediates in the "catecholamine cascade", that is, the pathway involved in synthesis of the neurotransmitter norepinephrine. Stepwise, these catecholamines are synthesized in the following manner: (1) tyrosine is 10 converted to dopa by the enzyme tyrosine hydroxylase; (2) dopa is converted to dopamine by the enzyme dopa decarboxylase; and (3) dopamine is converted to norepinephrine by the enzyme dopamine- β -hydroxylase. Inhibition of dopamine- β -hydroxylase activity, in 15 particular, would increase the renal vasodilatory, diuretic and natriuretic effects due to dopamine. Inhibition of the action of any of these enzymes would decrease the renal vasoconstrictive, antidiuretic and antinatriuretic effects of norepinephrine. Therapeutically, these effects oppose 20 chronic sodium retention.

Many compounds are known to inhibit the action of the catecholamine-cascade-converting enzymes. For example, the compound α -methyltyrosine inhibits the action of the enzyme tyrosine hydroxylase. The compound α -methyldopa inhibits the action of the enzyme dopadecarboxylase, and the compound fusaric acid inhibits the action of dopamine- β -hydroxylase. Such inhibitor compounds often cannot be administered systemically because of the adverse side effects induced by such compounds. For example, the desired therapeutic effects of dopamine- β -hydroxylase inhibitors, such as fusaric acid, may be offset by hypotension-induced compensatory stimulation of the

renin-angiotensin system and sympathetic nervous system, which promote sodium and water retention.

To avoid such systemic side effects, drugs may be targetted to the kidney by creating a conjugate compound that would be a renal-specific prodrug containing the targetted drug modified with a chemical carrier moiety. Cleavage of the drug from the carrier moiety by enzymes predominantly localized in the kidney releases the drug in the kidney. Gamma glutamyl transpeptidase and acylase are examples of such cleaving enzymes found in the kidney which have been used to cleave a targetted drug from its prodrug carrier within the kidney.

Renal targetted prodrugs are known for delivery 15 of a drug selectively to the kidney. For example, the compound L-y-glutamyl amide of dopamine when administered to dogs was reported to generate dopamine in vivo by specific enzymatic cleavage by γ -glutamyl transpeptidase [J. J. Kyncl et al, Adv. Biosc., 20, 369-380 (1979)]. In 20 another study, γ -glutamyl and N-acyl- γ -glutamyl derivatives of the anti-bacterial compound sulfamethoxazole were shown to deliver relatively high concentrations of sulfamethoxazole to the kidney which involved enzymatic cleavage. of the prodrug by acylamino acid deacylase and γ -glutamyl 25 transpeptidase [M. Orlowski et al, J. Pharmacol, Exp. Ther., 212, 167-172 (1980)]. The N- γ -glutamyl derivatives of 2-, 3-, or 4-aminophenol and p-fluoro-L-phenylalanine have been found to be readily solvolyzed in vitro by Yglutamyl transpeptidase [S.D.J. Magnan et al, J. Med. 30 Chem., 25, 1018-1021 (1982)]. The hydralazine-like vasodilator 2-hydrazino-5-g-butylpyridine (which stimulates guanylate cyclase activity) when substituted with the Nacetyl-\(\gamma \) glutamyl residue resulted in a prodrug which provided selective renal vasodilation [K. G. Hofbauer et

al, J. Pharmacol. Exp. Ther., 212, 838-844 (1985)]. The dopamine prodrug γ-L-glutamyl-L-dopa ("gludopa") has been shown to be relatively specific for the kidney and to increase renal blood flow, glomerular filtration and urinary sodium excretion in normal subjects [D. P. Worth et al, Clin. Sci. 69, 207-214 (1985)]. In another study, gludopa was reported to an effective renal dopamine prodrug whose activity can be blocked by the dopa-decarboxylase inhibitor carbidopa [R. F. Jeffrey et al, Br. J. Clin.
Pharmac., 25, 195-201 (1988)].

BRIEF DESCRIPTION OF THE DRAWING FIGURES

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Figure 1 shows the acute effects of i.v. injection of vehicle and Example #3 conjugate on mean arterial pressure in rats.

20 Figure 2 shows the acute effects of i.v. injection of vehicle and Example #3 conjugate on renal blood flow in rats.

Figure 3 shows the chronic effects of i.v.
25 infusion of vehicle and Example #464 conjugate on mean arterial pressure in spontaneously hypertensive rats.

Figure 4 shows time-dependent formation of the dopamine-\(\beta\)-hydroxylase inhibitor fusaric acid from the Example #859 conjugate incubated with rat kidney homogenate.

Figure 5 shows time-dependent formation of fusaric acid from the Example #859 conjugate incubated with

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a mixture of purified acylase I and gamma-glutamyl transpeptidase at pH 7.4 and 8.1.

Figure 6 shows the concentration-dependent

5 effect of fusaric acid and the Example #859 conjugate on norepinephrine production by dopamine-ß-hydroxylase in vitro.

Figure 7 shows dopamine-ß-hydroxylase inhibition 10 in vitro by fusaric acid, the Example #859 conjugate and possible metabolites at a concentration of 20 µM.

Figure 8 shows the acute effects of i.v.
injection of fusaric acid and Example #859 conjugate on
mean arterial pressure in spontaneously hypertensive rats.

Figure 9 shows the acute effects of i.v. injection of fusaric acid and Example #859 conjugate on renal blood flow in spontaneously hypertensive rats.

Figure 10 shows the effects of chronic i.v. infusion of vehicle, fusaric acid, and Example #859 conjugate for 5 days on mean arterial pressure in

spontaneously hypertensive rats.

Figure 11 shows the effects of chronic i.v. infusion of vehicle and Example #863 conjugate for 4 days on mean arterial pressure in spontaneously hypertensive rats.

Figure 12 shows the heart tissue concentrations of norepinephrine following the 5 day infusion experiment described in Figure 10.

Figure 13 shows the kidney tissue concentrations of norepinephrine following the 5 day infusion experiment described in Figure 10.

Figure 14 shows the effects of Example #859 conjugate on mean arterial pressure in anesthetized dogs after i.v. injection at three doses, plus vehicle.

Figure 15 shows the effects of Example #859

10 conjugate on renal blood flow in anesthetized dogs after i.v. injection at three doses, plus vehicle.

Figure 16 shows the effects of Example #858 conjugate on mean arterial pressure in conscious DOCA

15 hypertensive micropigs after i.v. infusion for three days.

DESCRIPTION OF THE INVENTION

Treatment of chronic hypertension or sodiumretaining disorders such as congestive heart failure,
cirrhosis and nephrosis, may be accomplished by
administering to a susceptible or afflicted subject a
therapeutically-effective amount of a renal-selective
prodrug capable of causing selective blockage of heightened
sympathetic nervous system effects on the kidney. An
advantage of such renal-selective prodrug therapy resides
in reduction or avoidance of adverse side effects
associated with systemically-acting drugs.

A renal-selective prodrug capable of providing renal sympathetic nerve blocking action may be provided by a conjugate comprising a first residue and a second residue connected together by a cleavable bond. The first residue

35 is derived from an inhibitor compound capable of inhibiting

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formation of a benzylhydroxyamine intermediate in the biosynthesis of an adrenergic neurotransmitter, and wherein said second residue is capable of being cleaved from the first residue by an enzyme located predominantly in the kidney.

The first and second residues are provided by precursor compounds having suitable chemical moieties which react together to form a cleavable bond between the first and second residues. For example, the precursor compound of 10 one of the residues will have a reactable carboxylic acid moiety and the precursor of the other residue will have a reactable amino moiety or a moiety convertible to a reactable amino moiety, so that a cleavable bond may be formed between the carboxylic acid moiety and the amino 15 moiety. An inhibitor compound which provides the first residue may be selected from tyrosine hydroxylase inhibitor compounds, dopa-decarboxylase inhibitor compounds, dopamine- β -hydroxylase inhibitor compounds, and mimics of any of these inhibitor compounds. 20

The inhibitor compounds described herein have been classified as tyrosine hydroxylase inhibitors, or as dopa-decarboxylase inhibitors, or as dopamine-β-hydroxylase inhibitors, for convenience of description. Some of the inhibitor compounds may be classifiable in more than one of these classes. For example, 2-vinyl-3-phenyl-2-aminopropionic acid derivatives are classified herein as tyrosine hydroxylase inhibitors, but such derivatives may also act as dopa-decarboxylase inhibitors. The term "inhibitor compound" means a compound of any of the three foregoing classes and which has the capability to inhibit formation of a benzylhydroxyamine intermediate involved in biosynthesis of an adrenergic neurotransmitter. Thus, a compound which does not inhibit formation of such

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benzylhydroxyamine intermediate is not embraced by the definition of "inhibitor compound" as used herein. For example, compounds which do not inhibit a benzylhydroxyamine intermediate are the compounds L-dopa and dopamine.

A class of compounds from which a suitable tyrosine hydroxylase inhibitor compound may be selected to provide the conjugate first residue is represented by Formula I:

$$A = \begin{bmatrix} R^1 \\ I \\ C \\ R^2 \end{bmatrix}_{m} \begin{bmatrix} R^3 & O \\ I & I \\ N-R^4 \\ H \end{bmatrix}$$
 (I)

wherein each of R¹ through R³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁴ selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R⁵ is selected from -OR 6 and

$$R^7$$
, wherein R^6 is selected from hydrido, alkyl,

cycloalkyl, cycloalkylalkyl, aralkyl and aryl, and wherein each of R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl,

alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein m is a number selected from zero through six;

5

wherein A is a phenyl ring of the formula

wherein each of R^9 through R^{13} is independently selected 10 from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, 15 thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy, formyl and a substituted or unsubstituted 5- or 6-membered heterocyclic ring selected from the group consisting of pyrrol-l-yl, 2carboxypyrrol-l-yl, imidazol-2-ylamino, indol-l-yl, 20 carbozol9-yl, 4,5-dihydro-4-hydroxy-4trifluoromethylthiazol3-yl, 4-trifluoromethylthiazol-2-yl, imidazol-2-yl and 4,5-dihydroimidazol-2-yl; wherein any two of the R⁹ through R¹³ groups may be taken together to form a benzoheterocylic ring selected from the group consisting 25 of indolin-5-yl, l-(N-benzoylcarbamimidoyl)indolin5-yl, lcarbamimidoylindolin-5-yl, lH-2-oxindol-5-yl, insol-5-yl, 2-mercaptobenzimidazol-5(6)-yl, 2-aminobenzimidazol-5-(6)yl, 2-methanesulfonamidobenzimidazol-5(6)-yl, lHbenzoxanol-2-on-6-yl, 2aminobenzothiazol-6-yl, 2-amino-4-30 mercaptobenzothiazol6-yl, 2,1,3-benzothiadiazol-5-yl, 1,3dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 1,3-dihydro1,3-dimethyl2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 4-methyl-2(H) oxoquinolin-6-yl, quinoxalin-6-yl, 2-hydroxyquinoxalin-6-yl, 2-hydroxquinoxalin-7-yl, 2,3-dihydroxyquinoxalin6-yl and 2,3-didydro-3(4H)-oxo-1,4-benzoxazin-7-yl; 5-hydroxy-4H-pyran-4-on-2-yl, 2-hydroxypyrid-4-yl, 2-aminopyrid-4-yl, 2-carboxypyrid-4-yl and tetrazolo-[1,5-a]pyrid-7-yl; and wherein A may be selected from

$$R^{15}$$
 R^{16}
 R^{16}
 R^{17}
 R^{18}
 R^{18}
 R^{19}
 R^{20}

10 and -N R²¹

15

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wherein each of R¹⁴ through R²⁰ is independently selected from hydrido, alkyl, hydroxy, hydroxyalkyl, alkoxy, cycloalkyl, cycloalkylalkyl, halo, haloalkyl, aryloxy, alkoxycarboxyl, aryl, aralkyl, cyano, cyanoalkyl, amino, monoalkylamino and dialkylamino, wherein each of R²¹ and R²² is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; or a pharmaceutically-acceptable salt thereof.

A preferred class of tyrosine hydroxylase 25 inhibitor compounds within Formula I is provided by compounds of Formula II:

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wherein each of R^1 and R^2 is hydrido; wherein m is one or two; wherein R^3 is selected from alkyl, alkenyl and alkynyl; wherein R^4 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R^5 is selected from $-OR^6$ and

-N , wherein R
6
 is selected from

hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R^7 and R^8 is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R9 through R13 is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, alkoxycarbonyl, alkoxy, arykoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, pyrrol-1-yl 2carboxypyrrol-1-yl, imidazol-2-ylamino, indol-1-yl, carbazol-9-yl, 4,5-dihydro-4-trifluoromethylthiazol-3-yl, 4-trifluoromethylthiazol-2-yl, imidazol-2-yl and 4,5dihydroimidazol-2-yl, and wherein any two of the R9 through R13 groups may be taken together to form a

benzoheterocyclic ring selected from the group consisting of indolin-5-yl, 1-(N-benzoylcarbamimidoyl)indolin-5-yl, 1-carbamimidoylindolin-5-yl, 1H-2-oxindol-5-yl, indol-5-yl, 2-mercaptobenzimidazol-5(6)-yl, 2-aminobenzimidazol5-(6)-yl, 2-methanesulfonamidobenzimidazol-5(6)-yl, 1H-benzoxanol-2-on-6-yl, 2-amino-benzothiazol-6-yl, 2-amino-4-mercaptobenzothiazol-6-yl, 2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-1,3-dimethyl-2,2-dioxo-2,1,3benzothiadiazol-5-yl, 4-methyl-10 2(H)-oxoquinolin-6-yl, quinoxalin-6-yl, 2-hydroxquinoxalin-7-yl, 2,3-dihydroxyquinoxalin-6-yl and 2,3-didydro-3(4H)-oxo-1,4-benzoxazin-7-yl; wherein R3 is -CH=CH2 or -C=CH; wherein R5 is selected from -OR6 and

15 $\frac{R^7}{R^8}$, wherein R^6 is selected from

hydrido, alkyl, hydroxy, hydroxyalkyl, alkoxy, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino; and wherein each of R7 and R⁸ independently is selected from hydrido, alkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; or a pharmaceutically-acceptable salt thereof.

A first sub-class of preferred tyrosine
hydroxylase inhibitor compounds consists of the following
specific compounds within Formula II:
4-cyanoamino-α-methylphenyalanine;
3-carboxy-α-methylphenylalanine;
3-cyano-α-methylphenylalanine methyl ester;
α-methyl-4-thiocarbamoylphenylalanine methyl ester;
4-(aminomethyl)-α-methylphenylalanine;
4-guanidino-α-methylphenylalanine;
3-hydroxy-4-methanesulfonamido-α-methylphenylalanine;
3-hydroxy-4-nitro-α-methylphenylalanine;

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4-amino-3-methanesulfonyloxy-\alpha-methylphenylalanine;
     3-carboxymethoxy-4-nitro-α-methylphenylalanine;
    α-methyl-4-amino-3-nitrophenylalanine;
    3, 4-diamino-\alpha-methylphenylalanine;
    α-methyl-4-(pyrrol-1-yl)phenylalanine;
 5
    4-(2-aminoimidazol-1-yl)-α-methylphenylalanine;
    4-(imidazol-2-ylamino)-\alpha-methylphenylalanine;
     4-(4,5-dihydro-4-hydroxy-4-trifluoromethyl-thiazol-2yl)-a-
    methylphenylalanine methyl ester;
    α-methyl-4-(4-trifluoromethylthiazol-2-yl)phenylalanine;
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    q-methyl-3-(4-trifluoromethylthiazol-2-yl)-phenylalanine;
    4-(imidazol-2-yl)-α-methylphenylalanine;
     4-(4,5-dihydroimidazol-2-yl)-\alpha-methylphenylalanine;
    3-(imidazol-2-yl)-\alpha-methylphenylalanine;
    3-(4,5-dihydroimidazol-2-yl)-a-methylphenylalanine;
15
     4-(imidazol-2-yl)phenylalanine;
     4,5-dihydroimidazol-2-yl)phenylalanine;
     3-(imidazol-2-yl)phenylalanine;
     3-(2,3-dihydro-1H-indol-4-yl)-\alpha-methylalanine;
    α-methyl-3-(lH-2-oxindol-5-yl)alanine;
     3-[1-(N-benzoylcarbamimidoyl)-2,3-dihydro-1Hindol-5-yl)-\alpha
    methylalanine;
     3-(1-carbamimidoyl-2,3-dihydro-1H-indol-5-yl-\alpha-
    methylalanine;
    3-(1H-indol-5-yl-\alpha-methylalanine;
25
     3-(benzimidazol-2-thione-5-yl)-\alpha-methylalanine;
     3-(2-aminobenzimidazol-5-yl-2-methylalanine;
     2-methyl-3-(benzoxazol-2-on-6-yl)alanine;
    3-(2-aminobenzothiazol-6-yl)-2-methylalanine;
     3-(2-amino-4-mercaptobenzothiazol-6-yl)-2methylalanine;
30
     3-(2-aminobenzothiazol-6-yl)alanine;
     2-methyl-3-(2,1,3-benzothiadiazol-5-yl)alanine;
     3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)-2methylalanine-
     2,2-dioxide;
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3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)-2-methylalanine-
    2,2-dioxide methyl ester;
     3-(1,3-dihydrobenzo-2,1,3-thiadiaxol-5-yl)alanine 2,2-
    dioxide;
    3-(1,3-dihydro-1,3-dimethylbenzo-2,1,3-thiadiazol-5yl-)-2-
    methylalanine 2,2-dioxide;
    \alpha-methyl-3-[4-methyl-2(lH)-oxoquinolin-6-yl]alanine;
     3-[4-methyl-2(lH)-oxoquinolin-6-yl]alanine;
    2-methyl-3-(quinoxalin-6-yl)alanine;
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    2-methyl-3-(2-hydroxyquinoxalin-6-yl)alanine;
     2-methyl-3-(2-hydroxyquinoxalin-7-yl)alanine;
     3-(2,3-dihydroxyquinoxalin-6-yl)-2-methylalanine;
     3-(quinoxalin-6-yl)alanine;
     3-(2,3-dihydroxyquinoxalin-6-yl)alanine;
15
    3-(1,4-benzoxazin-3-one-6-yl)-2-methylalanine;
     3-(1,4-benzoxazin-3-one-7-yl)alanine;
     3-(5-hydroxy-4H-pyran-4-on-2-yl)-2-methylalanine;
     3-(2-hydroxy-4-pyridyl)-2-methylalanine;
     3-(2-carboxy-4-pyridyl)-2-methylamine;
20
    α-methyl-4-(pyrrol-1-yl)phenylalanine;
    α-ethyl-4-(pyrrol-1-yl)phenylalanine;
     α-propyl-4-(pyrrol-l-yl)phenylalanine;
     4-[2-(carboxy)pyrrol-1-yl)phenylalanine;
    α-methyl-4-(pyrrol-l-yl)phenylalanine;
25
    3-hydroxy-\alpha-4-(pyrrol-l-yl) phenylalanine;
     3-methoxy-\alpha-4-(pyrrol-l-yl)phenylalanine;
     4-methoxy-\alpha-3-(pyrrol-1-yl)phenylalanine;
     4-(indol-l-yl)-\alpha-methylphenylalanine;
     4-(carbazol-9-yl)-\alpha-methylphenylalanine;
    2-methyl-3-(2-methanesulfonylamidobenzimidazol-5-
30
    vl)alanine;
     2-methyl-3-(2-amino-4-pyridyl)alanine;
    2-methyl-3[tetrazolo-(1,5)-\alpha-pyrid-7-yl]alanine;
    D, L-\alpha-\beta-(4-hydroxy-3-methyl) phenylalanine;
    D, L-\alpha-\beta-(4-hydroxy-3-phenyl) phenylalanine;
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D, L-\alpha-\beta-(4-hydroxy-3-benzyl) phenylalanine;
     D, L-\alpha-\beta-(4-methoxy-3-cyclohexyl) phenylalanine;
     \alpha, \beta, \beta trimethyl-\beta-(3,4-dihydroxyphenyl) alanine;
     \alpha, \beta, \beta trimethyl-\beta-(4-hydroxyphenyl)alanine;
     N-methyl \alpha, \beta, \beta trimethyl-\beta-(3,4-dihydroxphenyl) alanine;
     D,L \alpha, \beta, \beta trimethyl-\beta-(3,4-dihyroxyphenyl)alanine;
     trimethyl-\beta-(3,4-dimethoxyphenyl)alanine;
     L-\alpha-methyl-\beta-3,4-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-3,4-dihydroxyphenylalanine;
     L-\alpha-propyl-\beta-3,4-dihydroxyphenylalanine;
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     L-\alpha-butyl-\beta-3, 4-dihydroxyphenylalanine;
     L-\alpha-methyl-\beta-2, 3-dihydroxphenylalanine;
     L-\alpha-ethyl-\beta-2, 3-dihydroxphenylalanine;
     L-\alpha-propyl-\beta-2,3-dihydroxphenylalanine;
     L-\alpha-butyl-\beta-2, 3-dihydroxphenylalanine;
15
     L-α-methyl-4-chloro-2, 3-dihydroxyphenylalanine;
     L-α-ethyl-4-chloro-2, 3-dihydroxyphenylalanine;
     L-\alpha-propyl-4-chloro-2,3-dihydroxyphenylalanine;
     L-α-butyl-4-chloro-2, 3-dihydroxyphenylalanine;
     L-\alpha-\text{ethyl-}\beta-4-\text{methyl-}2, 3-dihydroxyphenylalanine;
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     L-\alpha-methyl-\beta-4-methyl-2,3-dihydroxyphenylalanine;
     L-\alpha-propyl-\beta-4-methyl-2,3-dihydroxyphenylalanine;
     L-\alpha-butyl-\beta-4-methyl-2, 3-dihydroxyphenylalanine;
     L-\alpha-methyl-\beta-4-fluoro-2, 3-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-4-fluoro-2, 3-dihydroxyphenylalanine;
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     L-\alpha-propyl-\beta-4-fluoro-2, 3-dihydroxyphenylalanine;
     L-\alpha-butyl-\beta-4-fluoro-2, 3-dihydroxyphenylalanine;
     L-\alpha-methyll-b-4-trifluoromethyl-2,3-dihydroxyphenylalanine
     L-\alpha-ethyl-\beta-4-trifluoromethyl-2,3-dihydroxyphenylalanine
     L-\alpha-propyl-\beta-4-trifluoromethyl-2,3-dihydroxyphenylalanine
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     L-\alpha-butyl-\beta-4-trifluoromethyl-2,3-dihydroxyphenylalanine
     L-\alpha-methyl-\beta-3,5-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-3,5-dihydroxyphenylalanine;
     L-\alpha-propyl-\beta-3,5-dihydroxyphenylalanine;
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 $L-\alpha$ -butyl- β -3,5-dihydroxyphenylalanine;

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L-\alpha-methyl-\beta-4-chloro-3,5-dihydroxphenylalanine;
      L-\alpha-ethyl-\beta-4-chloro-3, 5-dihydroxphenylalanine;
      L-\alpha-propyl-\beta-4-chloro-3,5-dihydroxphenylalanine;
      L-\alpha-butyl-\beta-4-chloro-3,5-dihydroxphenylalanine;
     L-\alpha-methyl-\beta-4-fluoro-3,5-dihydroxyphenylalanine;
      L-\alpha-ethyl-\beta-4-fluoro-3,5-dihydroxyphenylalanine;
      L-\alpha-propyl-\beta-4-fluoro-3,5-dihydroxyphenylalanine;
      L-\alpha-butyl-\beta-4-fluoro-3,5-dihydroxyphenylalaninei
     L-\alpha-methyl-\beta-4-trifluoromethyl-3,5-dihydroxyphenylalanine;
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     L-\alpha-ethyl-\beta-4-trifluoromethyl-3,5-dihydroxyphenylalanine;
     L-\alpha-propyl-\beta-4-trifluoromethyl-3,5-dihydroxyphenylalanine;
     L-\alpha-butyl-\alpha-4-trifluoromethyl-3,5-dihydroxyphenylalanine;
     L-\alpha-methyl-2,5-dihydroxphenylalanine;
     L-\alpha-ethyl-2,5-dihydroxphenylalanine;
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     L-\alpha-propyl-2,5-dihydroxphenylalanine;
     L-\alpha-butyl-2,5-dihydroxphenylalanine;
     L-\alpha-methyl-\beta-4-chloro-2,5-dihydroxyphenylalanine;
     L-\alpha-\text{ethyl}-\beta-4-\text{chloro-2}, 5-dihydroxyphenylalanine;
     L-\alpha-propyl-\beta-4-chloro-2, 5-dihydroxyphenylalanine;
     L-\alpha-butyl-\beta-4-chloro-2,5-dihydroxyphenylalanine;
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     L-\alpha-methyl-\beta-4-chloro-2,5-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-4-chloro-2, 5-dihydroxyphenylalanine;
     L-\alpha-propyl-\beta-4-chloro-2, 5-dihydroxyphenylalanine;
     L-\alpha-butyl-\beta-4-chloro-2,5-dihydroxyphenylalanine;
     L-\alpha-methyl-\beta-methyl-2,5-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-methyl-2,5-dihydroxyphenylalanine;
     L-\alpha-propyl-\beta-methyl-2,5-dihydroxyphenylalanine;
     L-\alpha-butyl-\beta-methyl-2,5-dihydroxyphenylalanine;
     L-\alpha-methyl-\beta-4-trifluoromethyl-2,5-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-4-trifluoromethyl-2,5-dihydroxyphenylalanine;
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     L-\alpha-propyl-\beta-4-trifluoromethyl-2,5-dihydroxyphenylalanine;
     L-\alpha-butyl-\beta-4-trifluoromethyl-2,5-dihydroxyphenylalanine;
     L-\alpha-methyl-\beta-3,4,5-trihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-3, 4, 5-trihydroxyphenylalanine;
35 L-\alpha-propyl-\beta-3, 4, 5-trihydroxyphenylalanine;
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L-\alpha-butyl-\beta-3, 4, 5-trihydroxyphenylalanine;
     L-\alpha-methyl-\beta-2,3,4-trihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-2,3,4-trihydroxyphenylalanine;
     L-\alpha-propyl-\beta-2, 3, 4-trihydroxyphenylalanine;
     L-\alpha-butyl-\beta-2, 3, 4-trihydroxyphenylalanine;
     L-\alpha-methyl-\beta-2,4,5-trihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-2,4,5-trihydroxyphenylalanine;
     L-\alpha-propyl-\beta-2,4,5-trihydroxyphenylalanine;
     L-\alpha-butyl-\beta-2,4,5-trihydroxyphenylalanine;
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     L-phenylalanine;
     D, L-\alpha-methylphenylalanine;
     D, L-3-iodophenylalanine;
     D, L-3-iodo-\alpha-methylphenylalanine;
     3-iodotyrosine;
     3,5-diiodotyrosine;
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     L-α-methylphenylalanine;
     D. L-\alpha-B- (4-hydroxy-3-methylphenyl) alanine;
     D. L-\alpha-\beta- (4-methoxy-3-benzylphenyl) alanine;
     D, L-\alpha-\beta- (4-hydroxy-3-benzylphenyl) alanine;
     D, L-\alpha-\beta-(4-methoxy-3-cyclohexylphenyl) alanine;
20
     D, L-\alpha-\beta-(4-hydroxy-3-cyclohexylphenyl) alanine;
     D, L-\alpha-\beta- (4-methoxy-3-methylphenyl) alanine;
     D. L-\alpha-\beta- (4-hydroxy-3-methylphenyl) alanine;
     N, O-dibenzyloxycarbonyl-D, L-\alpha-\beta- (4-hydroxy-3-
25
     methylphenyl) alanine;
     N, O-dibenzyloxycarbonyl-D, L-\alpha-\beta- (4-hydroxy-3-
     methylphenyl) alanine amide;
     D, L-\alpha-\beta-(4-hydroxy-3-methylphenyl) alanine amide;
     N, O-diacetyl-D, L-\alpha-\beta-(4-hydroxy-3-methylphenyl) alanine;
     D, L-N-acetyl-\alpha-\beta-(4-hydroxy-3-methylphenyl) alanine;
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     L-3, 4-dihydroxy-\alpha-methylphenylalanine;
     L-4-hydroxy-3-methoxy-\alpha-methylphenylalanine;
     L-3, 4-methylene-dioxy-\alpha-methylphenylalanine;
     2-vinyl-2-amino-3-(2-methoxyphenyl) propionic acid;
     2-vinyl-2-amino-3-(2,5-dimethoxyphenyl)propionic acid;
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2-vinyl-2-amino-3-(2-imidazolyl)propionic acid;
     2-vinyl-2-amino-3-(2-methoxyphenyl)propionic acid ethyl
     ester;
     \alpha-methyl-\beta-(2,5-dimethoxyphenyl)alanine;
     \alpha-methyl-\beta-(2,5-dihydroxyphenyl) alanine;
     \alpha-ethyl-\beta-(2,5-dimethoxyphenyl) alanine;
     \alpha-ethyl-\beta-(2,5-dihydroxyphenyl) alanine;
     \alpha-methyl-\beta-(2,4-dimethoxyphenyl)alanine;
     \alpha-methyl-\beta-(2, 4-dihydroxyphenyl) alanine;
     \alpha-ethyl-\beta-(2, 4-dimethoxyphenyl) alanine;
10
     \alpha-ethyl-\beta-(2,4-dihydroxyphenyl)alanine;
     \alpha-methyl-\beta-(2,5-dimethoxyphenyl)alanine ethyl ester;
     2-ethynyl-2-amino-3-(3-indolyl)propionic acid;
     2-ethynyl-2, 3-(2-methoxyphenyl) propionic acid;
     2-ethynyl-2,3-(5-hydroxyindol-3-yl)propionic acid;
15
     2-ethynyl-2-amino-3-(2,5-dimethoxyphenyl)propionic acid;
     2-ethynyl-2-amino-3-(2-imidazolyl) propionic acid;
     2-ethynyl-2-amino-3-(2-methoxyphenyl)propionic acid ethyl
     ester;
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     3-carbomethoxy-3-(4-benzyloxybenzyl)-3-aminoprop-1-yne;
     α-ethynyltyrosine hydrochloride;
     \alpha-ethynyltyrosine;
     α-ethynyl-m-tyrosine;
     \alpha-ethynyl-\beta-(2-methoxyphenyl) alanine;
     \alpha-ethynyl-\beta-(2,5-dimethoxyphenyl)alanine; and
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     \alpha-ethynylhistidine.
```

A second sub-class of preferred tyrosine
hydroxylase inhibitor compounds consists of compounds
wherein at least one of R¹⁰, R¹¹ and R¹² is selected from
hydroxy, alkoxy, aryloxy, aralkoxy and alkoxycarbonyl. More
preferred compounds of this second sub-class are
α-methyl-3-(pyrrol-l-yl)tyrosine;
α-methyl-3-(4-trifluoromethylthiazol-2-yl)tyrosine;
3-(imidazol-2-yl)-α-methyltyrosine;

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La-m-tyrosine;
    . L-α-ethyl-m-tyrosine;
     L-\alpha-propyl-m-tyrosine;
     L-\alpha-butyl-m-tyrosine;
 5 Lα-p-chloro-m-tyrosine;
     L-α-ethyl-p-chloro-m-tyrosine;
     L-α-butyl-p-chloro-m-tyrosine;
     Lα-p-bromo-m-tyrosine;
     L-α-ethyl-p-bromo-m-tyrosine;
     L-α-butyl-p-bromo-m-tyrosine;
10
     Lα-p-fluoro-m-tyrosine;
     Lα-p-iodo-m-tyrosine;
     L-α-ethyl-p-iodo-m-tyrosine;
     La-p-methyl-m-tyrosine;
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    La-p-ethyl-m-tyrosine;
     L-\alpha-ethyl-p-ethyl-m-tyrosine;
     L-α-ethyl-p-methyl-m-tyrosine;
     La-p-butyl-m-tyrosine;
     La-p-trifluoromethyl-m-tyrosine;
20
    L-3-iodotyrosine;
     L-3-chlorotyrosine;
     L-3,5-diiodotyrosine;
     L-\alpha-methyltyrosine;
    D, L-\alpha-methyltyrosine;
25
    D, L-3-iodo-\alpha-methyltyrosine;
    L-3-bromo-\alpha-methyltyrosine;
     D, L-3-bromo-\alpha-methyltyrosine;
     L-3-chloro-\alpha-methyltyrosine;
    D, L-3-chloro-\alpha-methyltyrosine; and
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     2-vinyl-2-amino-3-(4-hydroxyphenyl)propionic acid.
```

Another preferred class of tyrosine hydroxylase inhibitor compounds within Formula I consists of compounds

wherein R^3 is selected from alkyl, alkenyl and alkynyl; wherein R^4 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein m is a number selected from zero through five, inclusive; wherein R^5 is selected from OR^6 and

-N
$$_{R^{\ell}}^{\mbox{\scriptsize R}^{7}}$$
 , wherein $^{\mbox{\scriptsize R}^{6}}$ is selected from

hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, alkoxycarbonyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

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A preferred sub-class of compounds within Formula III consists of compounds wherein at least one of R^{10} , R^{11} and R^{12} is selected from hydroxy, alkoxy, aryloxy, aralkoxy and alkoxycarbonyl. More preferred compounds of

this sub-class are methyl(+)-2-(4-hydroxyphenyl)glycinate; isopropyl and 3-methyl butyl esters of (+)-2-(4hydroxyphenyl) glycine; (+)-2-(4-hydroxyphenyl) glycine; (-)-2-(4-hydroxyphenyl)glycine; (+)-2-(4-methoxyphenyl-glycine; and (+)-2-(4-hydroxyphenyl) glycinamide.

Still another preferred class of tyrosine hydroxylase inhibitor compounds within Formula I is provided by compounds of Formula IV:

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wherein each of R^1 and R^2 is hydrido; wherein m is a number selected from zero through five, inclusive; wherein R3 is selected from alkyl, alkenyl and alkynyl; wherein R4 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, 25 arylsulfinyl and arylsulfonyl; wherein each of R14 through R17 is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, 30 carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl.

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A preferred sub-class of compounds within Formula IV consists of L-α-methyltryptophan; D,L-5-methyltryptophan; D,L-5-chlorotryptophan; D,L-5-bromotryptophan; D,L-5-iodotryptophan; L-5-

hydroxytryptophan; D,L-5-hydroxy- α -methyltryptophan; α -ethynyltryptophan; 5-methoxymethoxy- α -ethynyltryptophan; and 5-hydroxy- α -ethynyltryptophan.

Still another preferred class of tyrosine

10 hydroxylase inhibitor compounds within Formula I is
provided by compounds wherein A is

$$-N$$
 , wherein R 6 is selected from R^{22}

three, inclusive. More preferred compounds in this class are 2-vinyl-2-amino-5-aminopentanoic acid and 2-ethynyl-2-amino-5-aminopentanoic acid.

Still another preferred class of tyrosine hydroxylase inhibitor compounds within Formula I is provided by compounds of Formula V:

wherein each of R^{23} and R^{24} is independently selected from hydrido, hydroxy, alkyl, cycloakyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl,

haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R25 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R²⁶ through R35 is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, alkoxy and formyl; wherein n is a number selected from zero through five, inclusive; or a pharmaceutically-acceptable salt thereof. A more preferred compound of this class is benzoctamine.

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A class of compounds from which a suitable dopadecarboxylase inhibitor compound may be selected to provide the conjugate first residue is represented by Formula VI:

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wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl,

hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl; wherein n is a number from zero through four; wherein each of \mathbb{R}^{43} and \mathbb{R}^{44} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, 10 monoalkylamino, dialkylamino, monoalkylcarbonylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, alkenyl, cycloalkenyl and alkynyl; wherein any R43 and R44 substituent having a substitutable position may be further substituted with one or more groups selected from 15 hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl; with the proviso that R^{43} and R^{44} cannot both be carboxyl at the same time, with the further proviso that when R^{36} is hydrido then R^{37} cannot be carboxyl, and with the further proviso that at least one of R43 through R44 is a primary or secondary amino group; or a 20 pharmaceutically-acceptable salt thereof.

A preferred class of compounds within Formula VI consists of compounds wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, 25 cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, 30 cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein n is a number from one through three; wherein each of R^{43} and R^{44} is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, amino, mono-35 alkylamino, dialkylamino, carboxyl, carboxyalkyl and

alkanoyl; and wherein any R^{43} and R^{44} substituent having a substitutable position may be further substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl.

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A more preferred class of compounds within Formula VI consists of those compounds wherein each of R³⁶ through R42 is independently selected from hydrido, hydroxy, alkyl, benzyl, phenyl, alkoxy, benzyloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, cyano, aminomethyl, carboxyl, carboxyalkoxy and formyl; wherein n is one or two; wherein each of \mathbb{R}^{43} and \mathbb{R}^{44} is independently selected from hydrido, alkyl, benzyl, phenyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl and alkanoyl; and wherein any R43. and R^{44} substituent having a substitutable position may be further substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl.

An even more preferred class of compounds within Formula VI consists of those compounds wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein n is one or two; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl and carboxyalkyl; and wherein any R⁴³ and R⁴⁴ substituted having a substitutable position may be further substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl.

A more highly preferred class of compounds within Formula VI consists of those compounds wherein each of ${\rm R}^{36}$ and ${\rm R}^{37}$ is hydrido and n is one; wherein each of ${\rm R}^{38}$ through R⁴² is independently selected from hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein each of R^{43} and R^{44} is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, 10 amino, monoalkylamino, carboxyl and carboxyalkyl; and wherein any R^{43} and R^{44} substituent having a substitutable position may be further substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl. Compounds of specific interest are (2,3,4-trihydroxy)-benzylhydrazine, 1-(D,L-15 seryl-2 (2, 3, 4-trihydroxybenzyl) hydrazine (Benserazide) and 1-(3-hydroxylbenzyl)-l-methylhydrazine.

Another more highly preferred class of compounds consists of those compounds wherein each of R^{36} and R^{37} is 20 independently selected from hydrido, alkyl and amino and n is two; wherein each of R^{38} through R^{42} is independently selected from hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; 25 wherein each of \mathbf{R}^{43} and \mathbf{R}^{44} is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl and carboxyalkyl. Compounds of specific interest are 2-hydrazino-2-methyl-3-(3,4-30 dihydroxyphenyl) propionic acid (Carbidopa), α -(monofluoromethyl)dopa, α -(difluoromethyl)dopa and α -methyldopa.

Another class of compounds from which a suitable dopa-decarboxylase inhibitor compound may be selected to

provide the conjugate first residue is represented by Formula VII

$$R^{46}$$
 R^{47}
 R^{48}
 R^{49}
 R^{50}
(VII)

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wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl and

CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, aryloxy, aralkoxy, amino, monoalkylamino and dialkylamino with the proviso that R⁴⁹ and R⁵⁰ cannot both be carboxyl at the same time, and with the further proviso that at least one of R⁴⁵ through R⁴⁸ is a primary or secondary amino group or a carboxyl group; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds within Formula VII consists of those compounds wherein each of R^{45} through R⁴⁸ is independently selected from hydrido, hydroxy,

alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl and alkanoyl and

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-CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, phenoxy, benzyloxy, amino, monoalkylamino and dialkylamino.

A more preferred class of compounds within

Formula VII consists of those compounds wherein each of R⁴⁵
through R⁴⁸ is independently selected from hydrido,
hydroxy, alkyl, benzyl, phenyl, alkoxy, benzyloxy,
alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino,
monoalkylamino, dialkylamino, carboxyl, carboxyalkyl,
alkanoyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and
formyl; wherein each of R⁴⁹ and R⁵⁰ s independently
selected from hydrido, alkyl, benzyl, phenyl, alkoxyalkyl,
haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino,
dialkylamino, carboxyalkyl and alkanoyl and

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CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, amino and monoalkylamino.

An even more preferred class of compounds of 30 Formula VII consists of those compounds wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl aminomethyl,

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carboxyalkoxy and formyl; wherein each of R^{49} and R^{50} is independently selected from hydrido, alkyl, amino, monoalkylamino, carboxyalkyl and

5 -CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, amino and monoalkylamino.

A highly preferred class of compounds within Formula VII consists of those compounds wherein each of R^{45} through R^{48} is independently selected from hydrido, hydroxy, alkyl, alkoxy and hydroxyalkyl; wherein each of R^{49} and R^{50} is independently selected from alkyl, amino, monoalkylamino, and

15 -CR⁵¹ wherein R⁵¹ is selected from hydroxy, methoxy, ethoxy, propoxy, butoxy, amino, methylamino and ethylamino.

A more highly preferred class of compounds within Formula VII consists of those compounds wherein said inhibitor compound is selected from endo-2-amino1,2,3,4-tetrahydro-1,2-ethanonaphthalene-2-carboxylic acid; ethylendo-2-amino-1,2,3,4-tetra-hydro-1,4-ethano-naphthalene-2-carboxylate hydrochloride; exo-2-amino1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylic acid; and ethyl-exo-2-amino-1,2,3,4-tetrahydro-1,4-ethano-naphthalene-2-carboxylate hydrochloride.

Another family of specific dopa-decarboxylase inhibitor compounds consists of 2,3-dibromo-4,4-bis(4-ethylphenyl)-2-butenoic acid; 3-bromo-4-(4-methoxyphenyl)-4-oxo-2-butenoic acid; N-(5'-phosphopyridoxyl)-L-3,4-dihydroxyphenylalanine; N-(5'-phosphopyridoxyl)-L-m-aminotyrosine;

- D, L- β -(3, 4-dihydroxyphenyl) lactate;
- D, L-β-(5-hydroxyindolyl-3) lactate;
- 2,4-dihydroxy-5-(1-oxo-2-propenyl)benzoic acid;
- 2,4-dimethoxy-5-[1-oxo-3-(2,3,4-trimethoxyphenyl-2-
- 5 propenyl]benzoic acid;
 - 2,4-dihydroxy-5-[l-oxo-3-(2-thienyl)-2-propenyl] benzoic acid;
 - 2,4-dihydroxy-5-[3-(4-hydroxyphenyl)-l-oxo-2-propenyl] benzoic acid;
- 10 5-[3-(4-chlorophenyl)-l-oxo-2-propenyl]-2,4-dihydroxy benzoic acid;
 - 2,4-dihydroxy-5-(1-oxo-3-phenyl-2-propenyl)benzoic acid;
 - 2,4-dimethoxy-5-[l-oxo-3-(4-pyridinyl)-2-propenyl] benzoic acid;
- 5-[3-(3,4-dimethoxyphenyl)-l-oxo-2-propenyl]-2,4 dimethoxy benzoic acid;
 - 2,4-dimethoxy-5-(1-oxo-3-phenyl-2-propenyl)benzoic acid; 5-[3-(2-furanyl)-1-oxo-2-propenyl]-2,4-dimethoxy benzoic
 - acid;
- 20 2,4-dimethoxy-5-[l-oxo-3-(2-thienyl)-2-propenyl] benzoic acid;
 - 2,4-dimethoxy-5-[3-(4-methoxyphenyl)-l-oxo-2-propenyl] benzoic acid;
 - 5-[3-(4-chlorophenyl)-1-oxo-2-propenyl]-2,4-dimethoxy
- 25 benzoic acid; and
 - 5-[3-[4-(dimethylamino)phenyl]-l-oxo-2-propenyl]-2,4 dimethoxy benzoic acid.

Another class of compounds from which a suitable dopa-decarboxylase inhibitor may be selected to provide the conjugate first residue is represented by Formula VIII:

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wherein R^{52} is selected from hydrido, OR^{64} and

$$R^{65}$$
, wherein R^{64} is selected from

hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and 15 phenyl, and wherein each of R⁶⁵ and R⁶⁶ is independently selected from hydrido, alkyl, alkanoyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl; wherein each of R⁵³, R⁵⁴ and R⁵⁷ through R⁶³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, 20 cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein each of ${\tt R}^{55}$ and ${\tt R}^{56}$ is independently selected from hydrido, alkyl, cycloalkyl, 25 cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, halo, haloalkyl, hydroxyalkyl and carboxyalkyl; wherein each of m and n is a number independently selected from zero through six, inclusive; or a pharmaceutically-acceptable salt thereof. 30

A preferred class of compounds of Formula VIII consists of those compounds wherein ${\tt R}^{52}$ is ${\tt OR}^{64}$ wherein ${\tt R}^{64}$

is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, benzyl and phenyl; wherein each of R⁵³, R⁵⁴ and R⁵⁷ through R⁶³ is independently selected from hydrido, alkyl, cycloalkyl, hydroxy, alkoxy, benzyl and phenyl; wherein each of R⁵⁵ and R⁵⁶ is independently selected from hydrido, alkyl, cycloalkyl, benzyl and phenyl; wherein each of m and n is a number independently selected from zero through three, inclusive.

- A more preferred class of compounds of Formula VIII consists of those compounds wherein R⁵² is OR⁶⁴ wherein R⁶⁴ is selected from hydrido and lower alkyl; wherein each of R⁵³ through R⁵⁸ is hydrido; wherein each of R⁵⁹ through R⁶³ is independently selected from hydrido, alkyl, hydroxy and alkoxy, with the proviso that two of the R⁵⁹ through R⁶³ substituents are hydroxy; wherein each of m and n is a number independently selected from zero through two, inclusive.
- 20 A preferred compound within Formula IX is 3-(3,4-dihydroxyphenyl)-2-propenoic acid, also known as caffeic acid.

Another class of compounds from which a suitable dopa-decarboxylase inhibitor compound may be selected to provide the conjugate first residue is a class of aromatic amino acid compounds comprising the following subclasses of compounds:

- amino-haloalkyl-hydroxyphenyl propionic acids,
 such as 2-amino-2-fluoromethyl-3hydroxyphenylpropionic acid;
- alpha-halomethyl-phenylalanine derivatives such as alpha-fluoroethylphenethylamine; and

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- indole-substituted halomethylamino acids.

Still other classes of compounds from which a suitable dopa-decarboxylase inhibitor compound may be selected to provide the conjugate first residue are as follows:

- isoflavone extracts from fungi and streptomyces, such as 3',5,7-trihydroxy-4',6dimethoxyisoflavone, 3',5,7-trihydroxy-4',8dimethoxyisoflavone and 3',8-dihydroxy-4',6,7trimethoxyisoflavone;
- sulfinyl substituted dopa and tyrosine derivatives such as shown in U.S. Patent No. 4,400,395 the content of which is incorporated herein by reference;
 - hydroxycoumarin derivatives such as shown in
 U.S. Patent No. 3,567,832, the content of
 which is incorporated herein by reference;
 - 1-benzylcyclobutenyl alkyl carbamate derivatives such as shown in U.S. Patent No. 3,359,300, the content of which is incorporated herein by reference;
 - arylthienyl-hydroxylamine derivatives such as shown in U.S. Patent No. 3,192,110, the content of which is incorporated herein by reference; and
- β-2-substituted-cyclohepta-pyrrol-8-1H-on-7-yl alanine derivatives.

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Suitable dopamine- β -hydroxylase inhibitors may be generally classified mechanistically as chelating-type inhibitors, time-dependent inhibitors and competitive inhibitors.

A class of compounds from which a suitable dopamine- β -hydroxylase inhibitor may be selected to provide the conjugate first residue consists of time-dependent inhibitors represented by Formula IX:

$$\begin{array}{c|c}
B & \begin{array}{c|c}
R^{67} \\
C \\
R^{68} \\
\end{array} & N \\
\end{array} \times \begin{array}{c}
R^{69} \\
H
\end{array} (IX)$$

wherein B is selected from aryl, an ethylenic moiety, an acetylenic moiety and an ethylenic or acetylenic moiety substituted with one or more radicals selected from substituted or unsubstituted alkyl, aryl and heteroaryl; wherein each of R⁶⁷ and R⁶⁸ is independently selected from hydrido, alkyl, alkenyl and alkynyl; wherein R⁶⁹ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is a number selected from zero through five.

A preferred class of compounds of Formula $I\dot{X}$ consists of those compounds wherein B is phenyl or hydroxyphenyl; wherein R^{67} is ethenyl or ethynyl; or an

acetylenic moiety substituted with an aryl or heteroaryl radical; and wherein n is a number from zero through three.

Another preferred class of compounds of Formula IX consists of those compounds wherein B is an ethylenic or 5 acetylenic moiety incorporating carbon atoms in the betaand gamma-positions relative to the nitrogen atom; and wherein n is zero or one. More preferred are compounds wherein the ethylenic or acetylenic moiety is substituted at the gamma carbon with an aryl or heteroaryl radical. 10 Even more preferred are compounds wherein said aryl radical is selected from phenyl, 2-thiophene, 3-thiophene, 2furanyl, 3-furanyl, oxazolyl, thiazolyl and isoxazolyl, any one of which radicals may be substituted with one or more groups selected from halo, hydroxyl, alkyl, haloalkyl, 15 cyano, alkoxy, alkoxyalkyl and cycloalkyl. More highly preferred are compounds wherein said aryl radical is selected from phenyl, hydroxyphenyl, 2-thiophene and 2furanyl; and wherein each of R67, R68 and R69 is hydrido.

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A family of specifically-preferred compounds within Formula IX consists of the compounds 3-amino-2-(2'-thienyl) propene; 3-amino-2-(2'-thienyl) butene; 3-(N-methylamino)-2-(2'-thienyl) propene; 3-amino-2-(3'-thienyl) propene; 3-amino-2-(2'furanyl) propene; 3-amino-2-(3'-furanyl) propene; 1-phenyl-3aminopropyne; and 3-amino-2-phenylpropene. Another family of specifically-preferred compounds of Formula VIII consists of the compounds (±)4-amino-3-phenyl-1butyne; (±)4-amino-3-(3'-hydroxyphenyl)-1-butyne; (±)4-amino3-phenyl-1-butene; (±)4-amino-3-(3'-hydroxyphenyl)-1-butene; and (±)4-amino-3-(4'-hydroxyphenyl)-1-butene.

Another class of compounds from which a suitable dopamine-\beta-hydroxylase inhibitor may be selected to provide the conjugate first residue is represented by Formula X:

wherein W is selected from alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl; wherein Y is selected from

$$-N \underbrace{ \begin{array}{c} Q \\ N-R^{70} \end{array} }$$

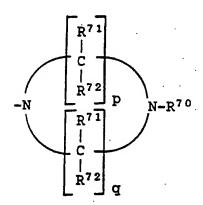
wherein R⁷⁰ is selected from hydrido, alkyl, cycloalkyl,
hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl,
aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino,
cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl,
alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each
of Q and T is one or more groups independently selected
from

$$\begin{bmatrix}
R^{71} \\
C \\
C \\
R^{72}
\end{bmatrix}, \quad
\begin{bmatrix}
R^{73} & R^{74} \\
C & C
\end{bmatrix}$$
and
$$\begin{bmatrix}
C & E & C
\end{bmatrix}$$

wherein each of R⁷¹ through R⁷⁴ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino,

monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds within Formula X consists of compounds wherein W is heteroaryl and Y is



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wherein R⁷⁰ is selected from hydrido, alkyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive.

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A more preferred class of compounds of Formula X consists of wherein R⁷⁰ is selected from hydrido, alkyl, amino and monoalkylamino; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number indpendently selected from two through four, inclusive. Even more preferred are compounds wherein R⁷⁰ is selected from hydrido, alkyl and amino; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, amino,

monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three. Most preferred are compounds wherein R^{70} is hydrido; wherein each of R^{71} and R^{72} is hydrido; and wherein each of p and q is two.

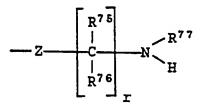
Another class of compounds from which a suitable dopamine- β -hydroxylase inhibitor may be selected to provide the conjugate first residue is represented by Formula XI:

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wherein E is selected from alkyl, cycloalkyl, alkenyl,
alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl,
aralkyl, heterocycloalkyl and heteroaryl; wherein F is
selected from

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wherein Z is selected from 0, S and N-R⁷⁸; wherein each of R⁷⁵ and R⁷⁶ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, minoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁷⁵ and R⁷⁶ may form oxo or thio; wherein r is a number selected from zero through six, inclusive; wherein each of R⁷⁷ and R⁷⁸ is independently selected from hydrido, alkyl, cycloalkyl,

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hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; or a pharmaceuticallyacceptable salt thereof.

Another class of compounds from which a suitable dopamine- β -hydroxylase inhibitor may be selected to provide the conjugate first residue is represented by Formula XII:

wherein each of R⁸² through R⁸⁵ is independently selected from hydrido, alkyl, haloalkyl, mercapto, alkylthio, cyano, alkoxy, alkoxyalkyl and cycloalkyl; wherein Y is selected from oxygen atom and sulfur atom; wherein each of R⁷⁹ and R⁸⁰ is independently selected from hydrido and alkyl; wherein R⁸¹ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein m is a number from one through six; or a pharmaceutically-acceptable salt thereof.

A preferred family of compounds of Formula XII consists of those compounds wherein each of R⁸² through R⁸⁵ is independently selected from hydrido, alkyl and haloalkyl; wherein Y is selected from oxygen atom or sulfur atom; wherein each of R⁷⁹, R⁸⁰ and R⁸¹ is independently

hydrido and alkyl; and wherein m is a number selected from one through four, inclusive.

A family of preferred specific compounds within 5 Formula XII consists of the following compounds: aminomethyl-5-n-butylthiopicolinate; aminomethyl-5-n-butylpicolinate; 2'-aminoethyl-5-n-butylthiopicolinate; 2'-aminoethyl-5-n-butylpicolinate; (2'-amino-1',1'-dimethyl)ethyl-5-n-butylthiopicolinate; 10 (2'-amino-1',1'-dimethyl)ethyl-5-n-butylpicolinate; (2'-amino-1'-methyl) ethyl-5-n-butylthiopicolinate; (2'-amino-1'-methyl)ethyl-5-n-butylpicolinate; 3'-aminopropyl-5-n-butylthiopicolinate; 3'-aminopropyl-5-n-butylpicolinate; 15 (2'-amino-2'-methyl)propyl-5-n-butylthiopicolinate; (2'-amino-2'-methyl)propyl-5-n-butylpicolinate; (3'-amino-1',1'-dimethyl) propyl-5-n-butylthiopicolinate; (3'-amino-1',1'-dimethyl) propyl-5-n-butylpicolinate; 20 (3'-amino-2',2'-dimethyl)propyl-5-n-butylthiopicolinate; (3'-amino-2',2'-dimethyl) propyl-5-n-butylpicolinate; 2'-aminopropyl-5-n-butylthiopicolinate; 2'-aminopropyl-5-n-butylpicolinate; 4'-aminobutyl-5-n-butylthiopicolinate; 25 4'-amino-3'-methyl)butyl-5-n-butylthiopicolinate; (3'-amino-3'-methyl)butyl-5-n-butylthiopicolinate;

and (3'-amino-3'-methyl)butyl-5-n-butylpicolinate.

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Another preferred class of compounds within Formula XII consists of those compounds of Formula XIII:

wherein each of R^{86} , R^{87} and R^{90} through R^{93} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, 15 aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁸⁶ and R⁸⁷ together may form oxo or thio; wherein r is a number selected from zero through six, 20 inclusive; wherein each of R⁸⁸ and R⁸⁹ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, 25 arylsulfinyl and arylsulfonyl.

A more preferred class of compounds within Formula XIII consists of those compounds wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein r is a number selected from zero through four, inclusive; wherein each of R⁸⁸ and R⁸⁹ is

independently selected from hydrido, alkyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl.

An even more preferred class of compounds within Formula XIII consists of those compounds wherein each of ${\rm R}^{86}$, ${\rm R}^{87}$ and ${\rm R}^{90}$ through ${\rm R}^{93}$ is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein r is a number selected from zero through three, inclusive; and wherein each of R^{88} and R^{89} is selected from hydrido, 10 alkyl, amino and monoalkylamino. Most preferred are compounds wherein each of R^{90} through R^{93} is independently selected from hydrido and alkyl; wherein each of R86 and ${\it R}^{87}$ is hydrido; wherein r is selected from zero, one and two; wherein R^{88} is selected from hydrido, alkyl and amino; 15 and wherein R^{89} is selected from hydrido and alkyl. Especially preferred within this class is the compound 5-nbutylpicolinic acid hydrazide (fusaric acid hydrazide) shown below:

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Another class of compounds from which a suitable dopamine-β-hydroxylase inhibitor compound may be selected to provide the conjugate first residue is represented by Formula XIV:

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$$\begin{array}{c}
R^{97} \\
R^{98}
\end{array}$$

$$\begin{array}{c}
R^{96} \\
R^{94}
\end{array}$$
(XIV)

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wherein each of R^{94} through R^{98} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, aryloxy, alkoxy, alkylthio, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, amido, alkylamido, hydroxyamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, tetrazolyl, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, formoyl and alkoxycarbonyl; with the proviso that at least one of R⁹⁴ through R⁹⁸ is

$$-\left(CH_{2}\right)_{1}A'$$

wherein A' is ${}^{\circ}CR^{99}$ or ${}^{\circ}N$ wherein ${}^{\circ}R^{99}$ is selected 25

from hydrido, alkyl, hydroxy, alkoxy, alkylthio, phenyl, phenoxy, benzyl, benzyloxy,

$$_{\rm -OR}100$$
 and -N $_{\rm R^{104}}^{\rm R^{103}}$, wherein $\rm R^{100}$ is selected from

hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenyl and benzyl; wherein each of R^{101} , R^{102} , R^{103} and R^{104} is 30

independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein t is a number selected from zero through four, inclusive; or a pharmaceutically-acceptable salt thereof.

A preferred family of compounds within Formula

XIV consists of those compounds characterized as chelatingtype inhibitors of Formula XV:

$$\begin{array}{c|c}
R^{97} & R^{96} \\
R^{98} & O \\
R^{10} & COR^{100}
\end{array}$$
(XV)

wherein each of R95 through R⁹⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, phenyl, benzyl, alkoxy, phenoxy, benzyloxy, alkoxyalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, amido, alkylamido, hydroxyamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, carboxyl, thiocarbamoyl, aminomethyl, nitro, formoyl, formyl and alkoxycarbonyl; and wherein R¹⁰⁰ is selected from hydrido, alkyl, phenyl and benzyl.

A class of specifically-preferred compounds of

Formula XV consists of

5-n-butylpicolinic acid (fusaric acid);

5-ethylpicolinic acid;

picolinic acid;

5-nitropicolinic acid;

5-aminopicolinic acid;

5-N-acetylaminopicolinic acid; 5-N-propionylaminopicolinic acid; 5-N-hydroxyaminopicolinic acid; 5-iodopicolinic acid; 5 5-bromopicolinic acid; 5-chloropicolinic acid; 5-hydroxypicolinic acid 5-methoxypicolinic acid; 5-N-propoxypicolinic acid; 5-N-butoxypicolinic acid; 10 5-cyanopicolinic acid; 5-carboxylpicolinic acid; 5-n-butyl-4-nitropicolinic acid; 5-n-butyl-4-methoxypicolinic acid; 5-n-butyl-4-ethoxypicolinic acid; 15 5-n-butyl-4-aminopicolinic acid; 5-n-butyl-4-hydroxyaminopicolinic acid; and 5-n-butyl-4-methylpicolinic acid.

20 Especially preferred of the foregoing class of compounds of Formula XV is the compound 5-n-butylpicolinic acid (fusaric acid) shown below:

Another class of compounds from which a suitable dopamine- β -hydroxylase inhibitor may be selected to provide the conjugate first residue consists of azetidine-2-carboxylic acid derivatives represented by Formula XVI:

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$$R^{109} - S - \begin{bmatrix} R^{108} \\ | \\ | \\ CH \end{bmatrix} + \begin{bmatrix} R^{107} & O & CH_2 \\ | & | \\ | & | \\ CH \end{bmatrix} + \begin{bmatrix} R^{106} \\ | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\ | & | \\$$

wherein R^{105} is hydrido, hydroxy, alkyl, amino and alkoxy; wherein R^{106} is selected from hydrido, hydroxy and alkyl; wherein each of R^{107} and R^{108} is independently selected from hydrido, alkyl and phenalkyl; wherein R^{109} is selected from hydrido and

from hydrido and

R¹¹⁰C- with R¹¹⁰ selected from alkyl, phenyl and phenalkyl; wherein u is a number from one to three, inclusive; and wherein v is a number from zero to two, inclusive; or a pharmaceutically-acceptable salt thereof.

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A preferred class of compounds within Formula XVI consists of those compounds wherein R^{105} is selected from hydroxy and lower alkoxy; wherein R^{106} is hydrido; wherein R^{107} is selected from hydrido and lower alkyl; wherein R^{108} is hydrido; wherein R^{109} is selected from hydrido and

R110 C- with R110 selected from lower alkyl and phenyl; wherein u is two; and wherein v is a number from zero to two, inclusive.

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A more preferred class of compounds within Formula XVI consists of those compounds of Formula XVII:

 $R^{109} S = \begin{bmatrix} CH_2 \\ V \end{bmatrix} V \begin{bmatrix} R^{107} & O \\ || & || \\ CR^{111} \end{bmatrix} (XVII)$

wherein R¹¹¹ is selected from hydroxy and lower alkyl; wherein R¹⁰⁷ is selected from hydrido and lower alkyl; wherein R¹⁰⁹ is selected from hydrido and

 R^{110} C- with R^{110} selected from lower alkyl and phenyl and v is a number from zero to two, inclusive.

A more preferred class of compounds within Formula XVII consists of those compounds wherein R^{111} is hydroxy; wherein R^{107} is hydrido or methyl; wherein R^{109} is hydrido or acetyl; and wherein n is a number from zero to two, inclusive.

Most preferred within the class of compounds of Formula XVII are the compounds 1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline and 1-(2-mercaptoacetyl)-L-proline (also known as captopril).

Another class of compounds from which a suitable dopamine- β -hydroxylase inhibitor compound may be selected to provide the conjugate first residue is represented by Formula XVIII:

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wherein each of R¹¹² through R¹¹⁹ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkyl, alkoxy, alkoxyalkyl, aralkyl, aryl, alkoxycarbonyl, hydroxyalkyl, halo, haloalkyl, cyano, amino, aminoalkyl, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, mercapto and alkylthio; or a pharmaceutically-acceptable salt thereof.

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A first preferred class of compounds within Formula XVIII consists of those compounds wherein R^{112} is selected from mercapto and alkylthio; wherein each of R^{113} and R^{114} is independently selected from hydrido, amino, aminoalkyl, monoalkylamino, monoalkylaminoalkyl, carboxyl and carboxyalkyl; wherein each of R^{115} and R^{119} is hydrido; and wherein each of R^{116} , R^{117} and R^{118} is independently selected from hydrido, hydroxy, alkyl, halo and haloalkyl; or a pharmaceutically-acceptable salt thereof.

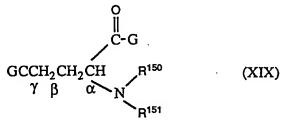
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A second preferred class of compounds within Formula XVIII consists of those compounds wherein R¹¹² is selected from amino, aminoalkyl, monoalkylamino, monoalkylaminoalkyl, carboxy and carboxyalkyl; wherein each of R¹¹³, R¹¹⁴, R¹¹⁵ and R¹¹⁹ is hydrido; and wherein each of R¹¹⁶, R¹¹⁷ and R¹¹⁸ is independently selected from hydrido, hydroxy, alkyl, halo and haloalkyl; or a pharmaceutically-acceptable salt thereof.

10 Compounds which fall within any of the aforementioned inhibitor compounds, but which lack a reactive acid or amino moiety to form a cleavable bond, may be modified or derivatized to contain such acid of amino moiety. Examples of classes of such compounds lacking an amino on acidic moiety are the following: 1-(3,5-dihaloaryl)imidazol-2-thione derivatives such as 1-(3,5-difluorobenzyl)imidazol-2-thione; and hydroxyphenolic derivatives such as resorcinol.

The second component of a conjugate of the invention is provided by a residue which forms a kidney-enzyme-cleavable bond with the residue of the first-component AII antagonist compound. Such residue is preferably selected from a class of compounds of Formula XIX:



wherein each of R¹⁵⁰ and R¹⁵¹ may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from

hydroxyl, halo, mercapto, $-0R^{152}$, $-SR^{153}$ and NR^{154} with each R^{152} , R^{153} and R^{154} is independently selected from hydrido and alkyl; with the proviso that said Formula XIX compound is selected such that formation of the cleavable bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula XIX compound.

More preferred are compounds of Formula XIX wherein each G is hydroxy.

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A more highly preferred class of compounds within Formula XIX consists of those compounds wherein each G is hydroxy; wherein ${\bf R}^{150}$ is hydrido; and wherein ${\bf R}^{151}$ is selected from

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-CR¹⁵⁵ wherein R¹⁵⁵ is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

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A most highly preferred compound of Formula XIX is N-acetyl- γ -glutamic acid which provides a residue for the second component of a conjugate of the invention as shown below:

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The phrase "terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino terminal moiety" characterizes a structural requirement for selection of a suitable angiotensin II antagonist compound as the "active" first residue of a conjugate of the invention.

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Such terminal amino moiety must be available to react with a terminal carboxylic moiety of the cleavable second residue to form a kidney-enzyme-specific hydrolyzable bond.

The first component used to form the conjugate of the invention provides a first residue derived from an inhibitor compound capable of inhibiting formation of a benzylhydroxylamine intermediate involved in the biosynthesis of an adrenergic neurotransmitter, hereinafter generally referred to as an "inhibitor compound". In one embodiment of the invention, the first component used to form a conjugate of the invention provides a first residue containing a terminal primary or secondary amino moiety. Examples of such terminal amino moiety are amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups such as aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

In another embodiment of the invention, the first 20 component used to form the conjugate of the invention provides a first residue derived from an inhibitor compound containing a moiety convertible to a primary or secondary amino terminal moiety. An example of a moiety convertible to an amino terminal moiety is a carboxylic acid group reacted with 25 hydrazine so as to convert the acid moiety to carboxylic acid hydrazide. The hydrazide moiety thus contains the terminal amino moiety which may then be further reacted with the carboxylic acid containing residue of the second component to form a hydrolyzable amide bond. Such hydrazide moiety thus 30 constitutes a "linker" group between the first and second components of a conjugate of the invention.

Suitable linker groups may be provided by a class of diamino-terminated linker groups based on hydrazine as defined by Formula XX:

wherein each of R^{200} and R^{201} may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, 10 dialkylamino, cyanoamino, carboxyalkyl, alkylsulfino, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive. In Table I there is shown a class of specific examples of diamino-terminated linker groups within Formula XX, identified as Linker Nos. 1-73. These linker groups would be suitable to 15 form a conjugate between a carbonyl moiety of an inhibitor compound residue (designated as "I") and a carbonyl moiety of a carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue 20 (designated as "T").

TABLE I

I = inhibitor
T = acetyl-γ-glutamyl

10	LINKER NO.	n	R ²⁰⁰	R ²⁰¹
15	1	0	Н	Н
15	2	0	СН3	Н
20	3	0	C2H5	Н
	4	0	С3Н7	Н
25	5	0	CH (CH3) 2	Н
30	6	0	C4H9	Н
	7	0 .	CH(CH3)CH2CH3	Н
35	8	0	C (CH3) 3.	Н
	9	0	С5Н9	Н
40	10	0	C6H ₁₁ (cyclo)	Н
45	11	.0	C6H5	Н
	12	0	CH ₂ C ₆ H ₅	Н
50	13	0	Н	CH ₃

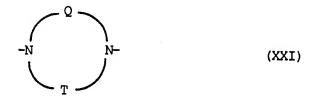
		LINKER NO.	n	R ²⁰⁰	R ²⁰¹
•		14	0	Н	C ₂ H ₅
•	5	15	0	Н	C3H7
		16	0	н	CH (CH ₃) ₂
	10	17	0	Н	C4H9
	15	18	0	н	СН (СН3) СН2СН3
		19	0	н	C (CH 3) 3
	20	20	0	н	С5Н9
		21	0	H	C6H13
	25	22	0	н	С6Н5
	30	23	0	н	CH2C6H5
		24	0	Н	C6H ₁₁ (cyclo)
	35	25	0	C6H13	Н
		26	0	CH3	CH3
•	40	27	0	С2Н5	C ₂ H ₅
• •	45	28	0	С3Н7	С3Н7
		29	0	CH (CH3) 2	CH (CH3) 2

	LINKER NO.	n	R ²⁰⁰	R ²⁰¹
	30	0	С4Н9	C4H9
5	31	0	CH (CH3) CH2CH3	СН (СН3) СН2СН3
	32 ·	0	C (CH 3) 3	C (CH3) 3
10	33	0	C5H9	С5Н9
	34	0	C6H13	C6H13
15	35	0	C6H ₁₁ (cyclo)	C6H ₁₁ (cyclo)
20	36 ·	0	C6H5	C6H5
20	37	0	CH2C6H5	СН2С6Н5
25	38	3 .	н	н
	39	3	СН3	н
30	40	3	Н	СН3
35	41	3	С6Н5	н
33	42	3	Н	C6H5
40	43	3	СНЗ	C6H5
	44	3	С6Н5	СН3

	LINKER NO.	n	R ²⁰⁰	R ²⁰¹
	45	3	CH2C6H5	Н
5	46	3	Н	CH2C6H5
	47	4	н	Н
10	48	4	СНЗ	Н -
15	49	4	Н	сн3
	50	4	С6Н5	н
20	51	4	Н	C6H5
	52	. 4	CH3	С6Н5
25	53	4	С6Н5	CH3
00	54	4	CH2C6H5	Н
30	55	4	Н	CH2C6H5
35	56	5	н	Н
	· 57	5	СНЗ	Н
40	58	5	н	СНЗ
	59	5	C6H5	н
45	60	5	Н	C6H5

	LINKER NO.	n	R ²⁰⁰	R ²⁰¹
	61	5	СН3	C6H5
5	62	5	C6H5	CH3
	63	5	CH2C6H5	H
10	64	5		CH ₂ C ₆ H ₅
٠	65	6	H	Н
15	66	6	СНЗ	Н
20	67	6	н	CH3
	68	6	C6H5	Н
25	. 69	6	Н	C6H5
	70	6	СНЗ	С6Н5
30	71	6	C ₆ H ₅	CH3
35	72	6	CH2C6H5	Н
	73	6	·H	CH2C6H5

Another class of suitable diamino terminal linker groups is defined by Formula XXI:



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wherein each of ${\tt Q}$ and ${\tt T}$ is one or more groups independently selected from

$$\begin{array}{c|c}
 & R^{202} \\
 & C \\
 & R^{203}
\end{array}$$
and
$$\begin{array}{c|c}
 & R^{204} & R^{205} \\
 & C & C
\end{array}$$

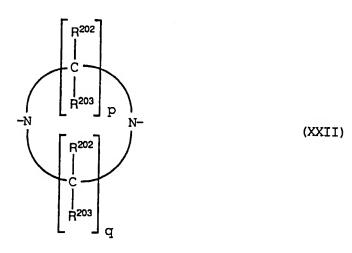
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wherein each of R²⁰² through R²⁰⁵ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

A preferred class of linker groups within Formula XX is defined by Formula XXII:

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wherein each of R²⁰² and R²⁰³ is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R²⁰² and R²⁰³ is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R²⁰² or R²⁰³ is attached in Formula XXII is not adjacent to a nitrogen atom of Formula XXII.

A more preferred class of linker groups of Formula XXII consists of divalent radicals wherein each of R^{202} and R203 is independently selected from hydrido, hydroxy, alkyl, 15 alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive. Even more preferred are linker groups wherein each of R^{202} and R^{203} is independently selected from hydrido, amino, monoalkylamino 20 and carboxyl; and wherein each of p and q is independently selected from the numbers two and three. Most preferred is a linker group wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two; such most preferred linker group is derived from a piperazinyl group and has the 25 structure



In Table II there is shown a class of specific examples of cyclized, diamino-terminated linker groups within Formula XXII. These linker groups, identified as Linker Nos. 74-95, would be suitable to form a conjugate between a carbonyl moiety of an inhibitor compound residue (designated as "I") and a carbonyl moiety of carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

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j. jE

TABLE II

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I = inhibitor $T = acetyl-\gamma-glutamyl$

10	LINKER NO.	R ²⁰⁶	R ²⁰⁷	R ²⁰⁸	R ²⁰⁹	R ²¹⁰	R ²¹¹	R ²¹²	R ²¹³
	74	Н	H	Н.	H	Н	Н	H ·	H
15	75	- СН3	Н	н	Н	Н	Н	Н	Н
20	76	Н	H.	Н	Н	CH3	Н	Н	Н
	77	СНЗ	Н	Н	Н	CH3	Н	Н	Н
25	78	СНЗ	Н	СНЗ	Н	Н	Н	Н	н
	79	СНЗ	Н	Н	H	Н	Н	СНЗ	H
30	80	СНЗ	СНЗ	н	Н	Н	Н	H	H
35	81	Н	Н	H	Н	СНЗ	СН3	Н	H
	82	СНЗ	СНЗ	Н	Н	CH3	СНЗ	н	H
40	83	СНЗ	СНЗ	СНЗ	СНЗ	H .	Н	н .	Н
	. 84	CH3	СНЗ	Н	. Н	Н	Н	CH3	СНЗ

	LINKER NO.	. R ²⁰⁶	R ²⁰⁷	R ²⁰⁸	R ²⁰⁹	R ²¹⁰	R ²¹¹	R ²¹²	R ²¹³
	85	н	Н	н	Н	СНЗ	СНЗ	СНЗ	СНЗ
5	86	C6H5	Н	Н	н	Н	Н	Н	Н
	87	н	Ħ	Н .	Н	C6H5	Н	н	Н
10	88	С6Н5	Н	Н	н	C6H5	Н	н .	Н
	89	C6H5	Н	Н	Н	Н	Н	C6H5	Н
15	90	C6H5	Н	C6H5	Н	Н	Н	Н	н
20	91	CH ₂ C ₆ H ₅	Н	Н	Н	Н	Н	Н	Н
20	92	Н	Н	Н	н	CH 2C6H5	Н	н	Н
25	93	CH ₂ C ₆ H ₅	Н	Н	Н	CH 2C6H5	н	Н	н
	94	CH2C6H5	Н	Н	н	Н	н	CH2C6H5	H
30	95	CH ₂ C ₆ H ₅	Н	CH2C6H5	Н	Н	Н	Н	н

Another class of suitable diamino terminal linker groups is defined by Formula XXIII:

$$-N = \begin{bmatrix} R^{214} & R^{216} \\ 1 & 1 \\ C & N \end{bmatrix} = \begin{bmatrix} R^{215} \\ 1 & 1 \\ N & N \end{bmatrix}$$
(XXIII)

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wherein each of R²¹⁴ through R²¹⁷ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfino, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

A preferred class of linker groups within Formula XXIII consists of divalent radicals wherein each of R²¹⁴ and 15 R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three. A more preferred class of linker groups within Formula XXIII consists of divalent radicals wherein each of 20 R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido and alkyl; and wherein p is two. A specific example of a more preferred linker within Formula XXIII is the divalent radical ethylenediamino. Table III there is shown a class of specific examples of 25 diamino-terminated linker gorups within Formula XXIII. linker groups, identified as Linker Nos. 96-134, would be suitable to form a conjugate between a carbonyl moiety of an inhibitor compound residue (designated as "I") and a carbonyl moiety of carbonyl terminated second residue such as the 30 carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

TABLE III

R²²⁰ R²²²
I I
I-N-C-C-N-T
I I I
R²¹⁸ R²²¹ R²²³ R²¹⁹

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I = inhibitor
G = acetyl-γ-glutamyl

10	LINKER NO.	R ²¹⁸	R ²¹⁹	R ²²⁰	R ²²¹	R ²²²	R ²²³	
	96	H	Н	н	Н	Н	Н	
15	97	н	Н	Н	н	н	СНЗ	
20	98	H	Н	Н	СНЗ	н	Н	
	99	Н	Н	н	СН3	Н	СНЗ	
25	100	CH3	н	н	Н	н -	Н	
	101	Н	СНЗ	Н	н	Н	Н	
30	102	Н	Н	н	Н	СНЗ	СНЗ	
35	103	Н	н	СНЗ	CH3	Н	Н	
	104	СНЗ	СНЗ	Н	Н	Н	Н	
40	105	н	Н	Н	Н	Н	С6Н5	
	106	Н	Н	Н	C6H5	Н	н	
45	107	н	Н	Н	C6H5	н	С6Н5	
	108	C6H5	Н	Н	Н	Н	Н	

						·		
	LINKER NO.	R ²¹⁸	R ²¹⁹	R ²²⁰	Ř ²²¹	R ²²²	R223	
			•					
	109	Н	C6H5	Н	H	Н	H	
5	110	Н	Н	-H	Н	С6Н5	C6H5	
)	111	Н	Н	C6H5	С6Н5	Н	Н	
	112	C6H5	C6H5	Н	Н	н	Н	
5	113	Н	Н	Н	H	н .	С2Н5	
	114	Н	Н	Н	С2Н5	н	H	
)	115	Н	н	Н	С2Н5	Н	С2Н5	
5	116	C2H5	Н	Н	Н	н	H	
	117	Н -	C2H5	н	н	Н	H	
)	118	Н	Н	Н	H	С2Н5	С2Н5	
	119	Н	н	C2H5	C2H5	Н	H	
	120	C2H5	C2H5	Н	H,	Н	H	
	121	CH3	Н	C6H5	Н	Н	H	
	122	CH3	Н	н	H	C6H5	Н	
i	123	н	СНЗ	C6H5	Н	Н	H	

	LINKER NO.	R ²¹⁸	R ²¹⁹	R220	R ²²¹	R 222	R ²²³
	124	Н	СНЗ	Н	Н	C6H5	5 H
5	125	СНЗ	СНЗ	Н	C6H5	Н	Н
	126	CH3	СНЗ	Н	н	Н	C6H5
10	127	Н	Н	Н	Н	Н	CH2C6H5
	128	Н	Н	Н	СН2С6Н5	Н	Н
15	129	CH2C6H5	Н	Н	Н	Н	Н
20	130	H.	CH2C6H5	Н	Н	н	Н
	131	CH3	Н	CH2C6H5	Н	Н	Н
25	132	СНЗ	Н	Н	н с	H2C6H5	Н
	133	Н	СНЗ	CH2C6H5	Н	Н	н
30	134	н	CH3	Н	H CI	H2C6H5	Н

The term "hydrido" denotes a single hydrogen atom (H). This hydrido group may be attached, for example, to an oxygen atom to form a hydroxyl group; or as another example, two hydrido groups may be attached to a carbon atom to form a divalent -CH2- group, that is, a "methylene" group; or as another example, one hydrido group may be attached to a carbon atom to form a trivalent —CH group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl", "aralkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or 10 branched radicals having one to about ten carbon atoms unless otherwise specifically described. Preferred alkyl radicals are "lower alkyl" radicals having one to about five carbon atoms. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl, 15 cyclobutyl, cyclohexyl and cycloheptyl. The term "haloalkyl" embraces radicals wherein any one or more of the carbon atoms is substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are 20 monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a fluoro atom within the group. Dihaloalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of 25 different halo groups. Examples of a dihaloalkyl group are dibromomethyl, dichloromethyl and bromochloromethyl. Examples of a polyhaloalkyl are trifluoromethyl, 2,2,2trifluoroethyl, perfluoroethyl and 2,2,3,3tetrafluoropropyl groups. The term "alkoxy", embraces linear or branched oxy-30 containing radicals having an alkyl portion of one to about ten carbon atoms, such as methoxy, ethoxy, isopropoxy and butoxy. The term "alkylthio" embraces radicals containing a linear or branched alkyl group, of one to about ten carbon atoms attached to a divalent sulfur atom, such as a 35 methythio group. The term "aryl" embraces aromatic radicals

such as phenyl, naphthyl and biphenyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, phenylbutyl and diphenylethyl. The terms "benzyl" and "phenylmethyl" are interchangeable. The terms "aryloxy" and "arylthio" denote radical respectively, aryl groups having an oxygen or sulfur atom through which the radical is attached to a nucleus, examples of which are phenoxy and phenylthio. The terms "sulfinyl" and "sulfonyl", whether used alone or linked to other terms, denotes respectively divalent 10 radicals >50 and >50, The term "acyl" whether used alone, or within a term such as acyloxy, denotes a radical provided by the residue after removal of hydroxyl from an organic acid, examples of such radical being acetyl and benzoyl. "Lower alkanoyl" is an example of a more preferred sub-class of acyl.

Within the classes of conjugates of the invention described herein are the pharmaceuticallyacceptable salts of such conjugates including acid addition 20 salts and base addition salts. The term "pharmaceuticallyacceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable 25 pharmaceutically-acceptable acid addition salts of conjugates of the invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate 30 organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, 35 gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic,

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benzoic, anthranilic, p-hydroxybenzoic, salicyclic, phenylacetic, mandelic, embonic (pamoic), methansulfonic, ethane sulfonic, 2-hydroxyethane sulfonic, pantothenic, benzene sulfonic, toluene sulfonic, sulfanilic, mesylic, cyclohexylaminosulfonic, stearic, algenic, β-hydroxy-butyric, malonic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of the conjugates include metallic salts made from aluminium, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding conjugates described herein by reacting, for example, the appropriate acid or base with the conjugate.

Conjugates of the invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting conjugates with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by

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conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active conjugates can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Synthetic Procedures

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Conjugates of the invention are synthesized by reaction between precursors of the first and second residues. One of such precursors must contain a reactive acid moiety, and the other precursor must contain a reactive amino moiety, so that a conjugate is formed having a cleavable bond. Either precursor of the first and second residues may contain such reactive acid or amino moieties. Preferably, the precursors of the first residue are inhibitors of benzylhydroxyamine biosynthesis and will contain a reactive amino moiety or a moiety convertible to a reactive amino moiety. Many of the tyrosine hydroxylase inhibitors and dopa-decarboxylase inhibitors are characterized in having a reactive amino moiety. Inhibitor compounds lacking a reactive amino moiety, such as the dopamine-β-hydroxylase inhibitor fusaric acid, may be chemically modified to provide such reactive amino moiety. Chemical modification of these inhibitor compounds lacking a reactive amino group may be accomplished by reacting an acid or an ester group on the inhibitor compound with an amino compound, that is, a compound having at least one reactive amino moiety and another reactive hetero atom selected from 0, S and N. A suitable amino compound would be a diamino compound such as hydrazine or urea. Hydrazine, for example, may be reacted with the acid or ester moiety of the inhibitor compound to form a hydrazide derivative of such inhibitor compound.

The dopamine-β-hydroxylase inhibitor compound 5-butyl-n-butylpicolinic acid (fusaric acid) may be used as a model compound to illustrate the chemical modification of an acid-containing inhibitor compound to make a reactive amino-containing precursor for synthesizing a conjugate of the invention. In the following General Synthetic Procedures, the substituents and reagents are defined as follows: each of R⁷⁹, R⁸⁰, R⁸¹, R⁸⁶, R⁸⁷, R⁸⁸, R⁸⁹ and R¹¹⁵ is as defined above; W is selected from alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl; and Z is selected from oxygen and sulfur. DCC is an abbreviation for dicyclohexylcarbodiimide.

General Synthetic Procedures

Procedure 1:

1. SOCl₂, MeOH

2. NaHCO₃

Procedure 2:

W-C-OH

Procedure 3:

Procedure 4:

Procedure 5:

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Procedure 6:

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Procedure 7:

The following Examples 1 through 1857 shown in Tables IV-XVII are highly preferred conjugates of the invention. These conjugates fall within three classes, namely, conjugates of tyrosine hydroxylase inhibitors of Tables IV-VI, conjugates of dopa-decarboxylase inhibitors of Tables VII-XI, and conjugates of dopamine-β-hydroxylase inhibitors of Tables XII-XVII. These conjugates may be prepared generally by the procedures outlined above in Schemes 1-7. Also, specific procedures for preparation of Examples 1-1857 are found in the conjugate preparations described in the examples appearing with the tables of conjugates.

The following Examples #1-#461 comprise three classes of highly preferred conjugates formed from tyrosine hydroxylase inhibitor compounds and glutamic acid derivatives. Examples #1-#3 are descriptions of specific preparations of such conjugates. Examples #4-#461, as shown in Tables IV-VI, may be prepared by procedures shown in these specific examples and in the foregoing general synthetic procedures of Schemes 1-7.

Example 1

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 $4-amino-4-carboxy-1-oxobutyl-\alpha-methyl-L-tyrosine$, methyl ester.

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Step. 1. Preparation of methyl α -methyl-L-tyrosinate, hydrochloride.

A solution of 11.0 g (56.4 mmol) of α -methyl-L-tyrosine in 100 mL of absolute methanol was cooled to 0°C and treated with 20.1 g (169 mmol) of thionyl chloride under a nitrogen atmosphere. The reaction was allowed to warm to ambient temperature and stir at reflux for 2 days. Concentration followed by trituration with 150 mL of ether gave 13.3 g (96%) of colorless product: NMR (DMSO-d₆) δ 1.49 (s, 3H), 3.02 (s, 2H), 3.73 (s, 3H), 6.73 (d, J = 11 Hz, 2H), 6.97 (d, J = 11 Hz, 2H), 8.50-8.70 (br s, 3H), 9.50 (s, 1H).

Step. 2. Preparation of 4-amino-4-carboxy-1-oxobutyl- α 25 methyl-L-tyrosine, methyl ester.

Under nitrogen, a solution of 35.1 g (116 mmol) of N-Boc-L- γ -glutanic acid- α -t-butyl ester (BACHEM) in 200 mL of methylene chloride was treated with 11.95 g (58 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction was allowed to stir for 2 hr prior to filtration under a nitrogen atmosphere. The methylene chloride was removed in vacuo and the residue

dissolved in 100 mL of anhydrous dimethylformamide (DMF). anhydride solution was slowly added to a solution of 7.0 g (29 mmol) of the α -methyl tyrosine ester from step 1 and 18.73 g (145 mmol) of diisopropylethylamine (DIEA) in 100 mL of anhydrous DMF. The reaction was allowed to stir overnight and was concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with cold 1M K2CO3 followed by water, dried (MgSO₄), and concentrated in vacuo to give the protected coupled product; a solution of this material in 150 mL of methylene chloride was cooled to 0°C and treated with 150 mL 10 of trifluoracetic acid (TFA) under nitrogen. The reaction was allowed to warm to ambient temperatures and stir overnight. Concentration in vacuo gave 4-amino-4-carboxy-1-oxobutyl- α methyl-L-tyrosine, methyl ester: NMR (DMSO-d₆) δ 1.20 (s, 3H), 1.90-2.20 (m, 2H), 2.23-2.38 (m, 2H), 2.95 (d, \underline{J} = 13 Hz, 15 1H), 3.26 (d, \underline{J} = 13 Hz), 3.57 (s, 3H), 3.92-4.06 (m, 1H), 7.06 (d, J = 9 Hz, 2H), 7.12 (d, J = 9 Hz, 2H).

Example 2

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N-[4-(acetylamino)-4-carboxy-1-oxobutyl]- α -methyl-L-tyrosine, methyl ester.

10 The compound of Example 1 was dissolved in 100 mL -of water and the pH adjusted to 9 with 1 M K2CO3. solution was cooled to 0°C and 3.30 mL (35 mmol) of acetic anhydride and 35 mL (35 mmol) of 1 M K₂CO₃ was added every 30 min. for 5 h; the pH was maintained at 9 and the reaction temperature kept below 5°C. After the last addition, the 15 reaction was allowed to warm to ambient temperature overnight. The pH was adjusted to 4 with 6 M HCl and concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) using isocratic 25% acetonitrile/water (0.05% 20 TFA) gave 9.0 g (82%) of colorless product: NMR (DMSO-d₆) δ 1.18 (s, 3H), 1.72-2.03 (m, 2H), 1.85 (s, 3H), 2.15 (t, $\underline{J} = 8$ Hz, 2H), 2.93 (d, $\underline{J} = 13$ Hz, 1H), 3.38 (d, $\underline{J} = 13$ Hz, 1H), 3.57 (s, 3H), 4.12-4.23 (m, 1H), 7.02 (d, J = 9 Hz, 2H), 7.09 (d, J = 9 Hz, 2H), 8.06 (s, 1H), 8.12 (d, J = 8 Hz, 1H).

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Example 3

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N-[4-(acetylamino)-4-carboxy-1-oxobutyl]-α-methyl-L-tyrosine

A solution of 9.0 g (23.7 mmol) of the compound of Example 2 in 225 mL of water was cooled to 0°C and treated 10 with 3.3 g (82.5 mmol) of solid NaOH in portions over 15 min. The reaction was stirred at 0-5°C overnight, the pH adjusted to pH 5 with 6N HCl, and concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) using isocratic 15% acetonitrite/water (0.05% TFA) gave 5.50 g (63%) 15 of colorless product: NMR (DMSO-d₆) δ 1.17 (s, 3H), 1.70-2.00 (m, 2H), 1.85 (s, 3H), 2.14 (t, $\underline{J} = 8$ Hz, 2H), 2.83 (d, $\underline{J} = 13$ Hz, 1H), 3.14 (d, J = 13 Hz, 1H), 4.12-4.23 (m, 1H), 6.56 (d, J = 9 Hz, 2H), 6.85 (d, J = 9 Hz, 2H), 7.69 (s, 1H), 8.12 (d, J = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 367 (70), 196 20 (52), 179 (58) 150 (100), 130 (80); HRMS. Calcd for M + H: 367.1505. Found: 367.1547. Anal. Calcd for $C_{17}H_{22}N_{2}O_{7} \cdot H_{2}O \cdot 0.125$ TFA: C, 52.00; H, 6.03; N, 7.03; F, 1.60. Found: C, 51.96; H, 6.25; N, 7.12; F, 1.60.

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The following Examples #4-#109 of Table IV are highly preferred conjugates formed from tyrosine hydroxylase inhibitor compounds and glutamic acid derivatives. These tyrosine hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula I and II, above.

TABLE IV

EXAMPLE NO.	R ¹	R ⁹	_R 10	R ¹¹	R12	R ⁵	E	P
4	СНЗ	Н	н	ОН	Н	OCH 3	СНЗ	сосн 3
5	CH3	H .	H	OН	Н	ОН	н	н
6	СНЗ	H	Н	OH	Н	OCH 3	СН3	н
7	СН3	Н	Н	ОН	Н	OH	СНЗ	Н
8	СНЗ	Н	н	OH	н	OH	СНЗ	сосн 3
9	CH ₂ F	Н	н	OH OH	Н	OCH 3	н	Н
10	CH ₂ F	Н	н	OH	Н	OCH 3	Н	COCH 3
11	CH ₂ F	Н	н	OH	н	OCH 3	СН3	Н
12	CH ₂ F	Н	Н	OH	Н	OCH 3	СН3	COCH 3
13	CH ₂ F	Н	Н	OH	Н	OH	Н	Н
14	CH ₂ F	Н	н .	OH	н	OH	Н	COCH 3

•								
EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ⁵	E	Р
15	CH ₂ F	Н	Н.	OH	Н	OH	СНЗ	Н
16	CH ₂ F	H	Н	OH	Н.	OH	СНЗ	COCH 3
17 .	CHF ₂	Н	Н	OH	Н	OCH 3	Н	H *****
18	CHF ₂	Н	. н	OH	H	OCH 3	Н	COCH 3
19	CHF 2	Н	Н	OH	Н	OCH 3	СНЗ	Н
20	CHF ₂	н	Н	OH	Н	OCH 3	СНЗ	COCH 3 _
21	CHF 2	Н	Н	OН	Н	OH	н	Н
22	CHF ₂	Н	н	OH	н	OH	н.	COCH 3
23	CHF 2	н	н	OH	Н	OH	СНЗ	Н
24	CHF ₂	н	Н	OH	Н .	OH	СНЗ	COCH 3
25	CF3	Н .	Н	OH	н	OCH 3	н .	H
26	CF3	Н	н .	OH	Н	OCH 3	Н	COCH 3
27	CF3	н	Н	OH	Н	OCH 3	СНЗ	H
28	CF3	Н	Н	OH	Н	OCH 3	СН3	сосн 3
29	CF3	Н	H	OH	Н	OH	. н	н
30	CÉ3	Н	Н	OH	Н	QH	Н	COCH 3

EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R11	R ¹²	R 5	E	P
31	CF3	Н	Н	OH	Н	OH	СНЗ	Н
32	CF3	Н	Н	OH	Н	ОН	СНЗ	сосн 3
33	С2Н5	Н	Н	OH	Н	OCH 3	Н	Н
34	C ₂ H ₅	Н	н	OН	Н	OCH 3	н	COCH 3
35	C ₂ H ₅	Н	Н	OH	н	осн 3	СН3	Н
36	С2Н5	Н	н	OH	Н	OCH 3	СНЗ	COCH 3
37	С2Н5	Н	Н	OH	н	OH	н	Н
38	С2Н5	Н	Н	OH	Н	ОН	н	COCH 3
39	С2Н5	Н	Н	OH	Н	ОH	СНЗ	Н
40	C2H5	Н	Н	OH	Н	OH	СНЗ	COCH 3
41	С3Н7	Н	H	OH	Н	OCH 3	Н	Н
42	С3Н7	Н	Н	OH	Н	OCH 3	Н	COCH 3
43	C3H7	H	Н	OH	Н	OCH 3	СНЗ	Н
44	С3Н7	Н	Н	OH	н	OCH 3	СНЗ	COCH 3
45	С3Н7	Н	Н	OH	Н	OH	Н	Н

			•						
EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ⁵	E	P	
46	С3Н7	Н	Н	OH.	н	OH	Н	COCH 3	
4 7	СЗН7	Н	Н	OH	н	OH	СНЗ	H	
48	C3H7	Н	н	OH	н .	OH	CH3	COCH 3	
49	CH3	Н	Н	NHCN	н	OH	Н	COCH 3	
50	СНЗ	Н	СО2Н	Н	Н	Н	OH	COCH 3	
51	CH3	Н	CN:	н	Н	OH	н	COCH 3	
52	СНЗ	Н	Н	CH2NH2	Н	OH	H	COCH 3	
53	CH3	Н	Н	CH2CH2CN	H	OH	н	COCH 3	
54	CH3	Н	ОН	CH3SO2NH	Н	OH	н	COCH 3	
55	СНЗ	Н	OH	NO2	Н	OH	Н	COCH 3	
56	СНЗ	Н	CH3 SO3	NH2	H .	OH	Н.	COCH 3	
57	СНЗ	Н	CO2 CH3	NO ₂	Н	OH	H.	COCH 3	
58	СНЗ	H	NO2	NH ₂	Н	OH	Н	COCH 3	
59	CH3	H	NH ₂	NH2	Н	OH	Н	COCH 3	•
60	СНЗ	Н	СНЗ	OH	Н	OH	Н	COCH 3	

EXAMPLE NO.	R ¹	R ⁹	R10	R ¹¹	R ¹²	R ⁵	E	P
61	СНЗ	Н	С6Н5	OH	Н	OH	Н	СОСНЗ
62	СНЗ	H	СН2С6Н5	OH	Н	OH	. Н	COCH 3
63	СНЗ	Н	C6H ₁₁ (cyclo)	СН30	H	OH	Н	COCH 3
64	СНЗ	OH	OH	Н	Н	OH	Н	COCH 3
65	СНЗ	OH	OH	Cl	Н	ОН	Н	COCH 3
66	СНЗ	OH	ОН	СНЗ	Н	OH	Н	COCH 3
67	СНЗ	OH	OH	F	Н	OH	Н	COCH 3
68	СНЗ	ОН	OH	CF3	Н	OH	н	COCH 3
69	СНЗ	Н	OH	Н	OH	OH	н	COCH 3
70	. СН3	Н	OH	Cl	OH	OH	Н	COCH 3
71	СНЗ	Н	OH	F	OH	OH	Н	COCH 3
72	СНЗ	H	ОН	CF3	OH	OH	Н	COCH 3
73	СНЗ	OH	н	Н	OH	OH	Н	COCH 3
74	СН3	OH	Н	Cl	OH	OH	Н	COCH 3
75	СНЗ	OH	н	СНЗ	OH	ОН	H.	COCH 3
76	CH3	OH	Н	CF3	ОН	OH	Н	COCH 3

EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R ¹¹	R ¹²	R 5	E	P
								:
77	СНЗ	Н	OH	OH .	OH .	OH	Н	COCH 3
78	СНЗ	OH	ОН	OH .	Н	OH	Н	COCH 3
7 9	СНЗ	ОH	Н	OH	OH	OH	н	COCH 3
80	СНЗ	Н	H	н	Н	OH	Н	COCH 3
81	H	Н	Н	Н	Н	OH	Н	COCH 3
82	Н	Н	ľ	.Н	н .	Ή	H	COCH 3
83	СНЗ	Н	I	Н	Н	Н	Н	COCH 3
84	Н	H	· I	OH	Н	Н	н	COCH 3
85	Н	- Н	I	Н	I	Н	Н	COCH 3
86	СНЗ	Н	СНЗ	OH	Н	H	Н .	COCH 3
87	СНЗ	Н	С6Н5СН2	CH30	н	Н	Н	COCH 3
88	СНЗ	Н	C6H5CH2	OH	Н	Н	Н	COCH 3
89	СНЗ	Н	C6H11 (cyclo)	СН30	Н	Н	Н	COCH 3
. 90	СНЗ	н	C ₆ H ₁₁ (cyclo)	OH	н .	Н	н.	COCH 3
91	СНЗ	Н	СНЗ	CH30	H	H	Н	сосн з

EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ⁵	E	Р
92	СНЗ	Н	СНЗ	OH	Н	Н	Н	сосн 3
93	СНЗ	н	CH3 C6	H5CH2CO2	Н	Н	Н	COCH 3
94	СН3	Н	СНЗ	OH	Н	Н	Н	сосн 3
95	СНЗ	Н	CH3 C6	H5CH2CO2	Н	Н	Н	сосн 3
96	СН3	Н	СНЗ	CH3CO2	Н	н	Н	COCH 3
97	СНЗ	Н	CH30	OH	Н	Н	Н	COCH 3
98	СНЗ	Н	-0CH ₂ () -	Н	Н	Н	COCH 3
99	СНЗ	CH30	Н	Н	СН30	Н	Н	COCH 3
100	СНЗ	OH	н	Н	OH	Н	Н	COCH 3
101	СНЗ	СНЗО	н	СН30	Н	Н	Н	COCH 3
102	CH3	OH	Н	OH	Н	Н	Н	COCH 3
103	CH3	СНЗО	Н	H	СН30	0С2Н5	Н	COCH 3
104	С≡СН	СНЗО	Н	н	Н	н	Н	сосн 3
105	С≡СН	СНЗО	Н	Н	СН3О	н	Н	COCH 3
106	С≔СН	Н	Н	OH	Н	н	Н	COCH 3

EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R ¹¹	R ¹²	Ŕ ⁵	E	P
107	С≔СН	Н	OH	Н	Н	H	H.	COCH 3
108	СН == CH ₂	СН30	Н .	H	H	Н	Н	COCH 3
109	СН = СН₂	CH30	Н	Н	CH30	Н	Н	COCH 3

The following Examples #110-#413 of Table V are highly preferred conjugates formed from tyrosine hydroxylase inhibitor compounds and glutamic acid derivatives. These tyrosine hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula I, above.

TABLE V

EXAMPLE	A	R ³	R 5	F.	D
NO.				_	•
					·

EXAMPLE NO.	A	R ³	R ⁵	E	P
114	H-Z-H	CH3	OH	H	Ħ
115	H-H	СН3	OH	Н	сосн 3
116		CH3	ОН	СНЗ	н

EXAMPLE NO.	A	R ³	R ⁵	E	P	
119	H-H	≈о сн₃	OCH 3	Н	сосн3	
120	H H	≻о снз	OCH 3	СНЗ	Н	
121	H-K-H	≻ О СН3	OCH 3	СН3	COCH 3	
122	N-H	≈ о сн₃	ОН	Н	Н	
123	T H	О СН3	OH	H	COCH 3	
•	\					

OH

СНЗ

Н

EXAMPLE	A	R ³	R ⁵	E	P	·
NO.						ليست

EXAMPLE NO.	Α	R ³	·R5	E	P	
130	H-H	СНЗ	OH	Н	н	
131	H-H	СН3	ОН	Н	COCH 3	
132	H H	СН3	ОН	СН3	H	
133	T N H	CH3	OH .	CH3	COCH3	
134	N N N I	¹ ₂ CH3	осн ₃	Н	н	
135	N N	IH₂ CH3	OCH 3	Н	сосн3	

EXAMPLE NO.	A	R ³	R ⁵	E	P	
136	\(\sigma_N^\)	⊢NH₂ CH3	OCH 3	СН3	Н	
137	TT,	⊢NH₂ CH3	CH 3	СНЗ	COCH 3	
138	N N	⊢NH₂ CH3	OН	Н	Н	
139	N N	⊢NH₂ CH3	OH	Н	COCH3	
140	N N	NH₂ CH3	. OH	СН3	н	
141	TTNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	⊢NH₂ CH3	OH	СН3	COCH3	
142		I-H CH3	OCH 3	H	Н	
143	II.	-H O CH3	OCH 3	н	COCH3	

EXAMPLE	' , A	R ³	R ⁵	E	P
NO.					

EXAMPLE NO.	A	R ³	R ⁵	E.	P	
151		−NH₂ CH3	OCH 3	н	сосн3	
152	(I)	−NH₂ CH3	OCH 3 .	CH3 .	Н	
153	(I)s	−NH ₂ CH3	OCH 3	СНЗ	COCH ₃	
154	(I)	−NH ₂ CH3	OH .	Н	н	
155	IIs	−NH ₂ CH3	OH	Н	COCH 3	
156	II.s	−NH _{2 CH3}	OH	СН3	Н	
157		−NH₂ CH3	OH	СН3	сосн3	

EXAMPLE NO.	A	R ³	R ⁵	E	P	
158	SH NH	. CH3	осн з	н	Н	
159	SH	₂ CH3	осн з	Н	СОСН3	
160	SH	₂ СН3	OCH 3	CH3	Н	
161	SH NH	₂ CH3	OCH 3	СНЗ	COCH3	
162	SH NH ₂	; CH3	OH	н	н	
163	SH S NH ₂	CH3	ОН	Н	сосн3	

EXAMPLE	A	R ³	R ⁵	E	P
NO.					

		•		
164	SH NH ₂ CH ₃	ΟΉ	CH3	Н
165	SH NH _z CH ₃	OH	CH3	соснз
166	NH ₂ CH ₃	OCH 3	Н	H
167	S NH ₂ CH ₃	OCH3	н	сосн3
168	NH ₂ CH ₃	OCH 3	СН3	H
169	NH ₂ CH ₃	OCH 3	СНЗ	COCH 3

OH

EXAMPLE	A	R ³	R ⁵	E	P
NO.					

		•		
171	NH ₂ CH ₃	ОН	н	сосн 3
172	NH ₂ CH ₃	ОН	СН3	н
173	NH ₂ CH ₃	ОН	СНЗ	сосн3
174	N-H CH3	OCH 3	Н	Н
175	N-H CH3	OCH 3	Н	сосн3
176	N-H CH3	OCH 3	СН3	Н
177	N-H CH3	OCH 3	СНЗ	COCH 3

EXAMPLE NO.	A	. R ³	R ⁵	E	P	
178	N-H S N-H	CH3	ОН	Н	H.	
179	N-H S N-H	CHO	OH	Н	COCH 3	
180	N-H	СНЗ	OH	СНЗ	H .	
181	N-H S N-H	CH3	OH.	СНЗ	COCH3	
182	CH ₃	_ O CH3	OCH 3	H	н	
183	CH ₃	O CH3	OCH 3	Н	сосн3	
184	CH ₃	_ O CH3	OCH 3	СН3	Н	

EXAMPLE	A	R ³	_R 5	P	6
NO.				E .	P .

EXAMPLE	A	R ³	R ⁵	E	P
NO.					

190 H OCH 3 H H

191 H CCCH3

192 H OCH 3 CH3 H

193 H OCH 3 CH3 COCH 3

EXAMPLE NO.	A	R ³	R ⁵	E	P
NO.					•

EXAMPLE NO.	A	R ³	R ⁵	E	P
198		CH3	осн 3	н .	Н
199		СН3	OCH 3	Н .	сосн3
200	N	СН3	OCH 3	СН3	Н
201	N_{N}	СН3	OCH 3	СНЗ	COCH 3
202	N	СН3	OH	н	Н
203	N	СНЗ	OH	н	COCH 3
204 ·	N	СНЗ	OH	СНЗ	H

EXAMPLE NO.	A	R ³	R ⁵	E	P
205	N N	СН3	OH	СНЗ	COCH3
206	II, N	ОН СН3	OCH 3	н	н
207	II, N	CH3	OCH 3	Н	сосн3
208		СН3	OCH 3	СНЗ	н
209	N OF	CH3	OCH 3	СНЗ	COCH 3
210	N	СНЗ	OH	Н	н
211	TINTO	н Сн ₃	OН	Н	сосн 3

EXAMPLE NO.	A	R ³	R ⁵	E	P
212	CIN'T	,ОН СН3	QΗ	СНЗ	Н
213	T N N	ÇH3	OH .	СН3	сосн3
214		OH CH3	осн з	н	H
215	L _N J	OH _{CH3}	OCH 3	н	сосн3
216	L _N J	OH CH3	OCH 3	СНЗ	Н
217	J _N J	OH CH3	OCH 3	СНЗ	сосн 3

EXAMPLE	A	R ³	R ⁵	E	P
NO.					

EXAMPLE NO.	A	R ³	R ⁵	E	P
223	N,	OH CH3	OCH 3	. Н	сосн3
224	N,	OH CH3	OCH 3	СНЗ	Н
225	N,	OH CH3	OCH 3	СН3	COCH 3
226	N,	OH CH3	OH	Н	н
227	N _N	OH CH3	OН	H	COCH 3
228	N.	OH CH3	OH	СНЗ	Н
229	N.	OH CH3	ОН	СН3	сосн3

EXAMPLE NO.	A	R3	R ⁵	E	P	
230		н	OCH 3	Н	Н	
231	N_{N}	Н	ОСН 3	н	сосн3	
232	N	н	OCH 3	СНЗ	Н	
233		н	OCH 3	СН3	COCH 3	
234		н	OН	H	н	
235	N	Н	OH ·	Н	COCH 3	

EXAMPLE NO.	A	R ³	R ⁵	Ε	P
236		H .	ОН	. СН3	н
237	N_{N}	н	ОН	СН3	COCH3
238		OH H	OCH 3	н	н
239	II, NI	он ^н	OCH 3	Н	соснз
240		OH H	OCH 3	СНЗ	H
241	N X	OH H	OCH 3	СН3	COCH 3
242	II, N	.он ^Н	OH	H	н

EXAMPLE NO.	A	R ³	R ⁵	E	P
243	II,	OH H	OН	H	COCH 3
244	N _N	OH H	СН	СН3	н
245	N N	OH H	OН	СН3	сосн3
246	H N H	CH3	OCH 3	н	н
247	N H	CH3	OCH 3	н	сосн3
248	N H	СН3	OCH 3	СНЗ	н

EXAMPLE	A	R ³	R ⁵	E	I	
NO.						

249 CH3 CCH3 CCH3

250 CH₃ CH₃ H H

251 CH₃ OH H COCH₃

252 CH₃ OH CH₃ H

253 CH₃ CH₃ COCH₃

EXAMPLE	A	R ³	R ⁵	E	P
NO.					

EXAMPLE NO.	A	R3	R 5	E	P
258	H-40	Н	OH	н	н
259	H N H	H .	OН	Н	COCH 3
260	H-N-H) _н	OΗ	CH3	н
261	H H	Н	ΟΉ	CH3	СОСН3
. 262	но	СН3	OCH 3	н	H

EXAMPLE	A	R ³	R 5	E	р
NO.					<u> </u>

263

СНЗ

OCH 3

Н

сосн3

264

СНЗ

OCH 3

СНЗ

H

265

СНЗ

OCH 3

СНЗ

3 COCH 3

266

СНЗ

OH

H

Н

COCH 3

267

СНЗ

OH

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
268	но	CH3	ОН	СН3	Н
269	но	CH3	OН	СНЗ	сосн3
270	ОН	СН3	OCH 3	н	Н
271	N OH	СН3	OCH 3	: H	сосн3

EXAMPLE	A	R ³	R ⁵	E.	D
NO.					-

282

EXAMPLE NO.	A	R ³	R ⁵	E	P
278	CO ₂ H	СНЗ	OCH 3	Н	Н
279	CO ₂ H	СНЗ	OCH 3	н	СОСН3
280	CO ₂ H	. СН3	OCH 3	СН3	н
281	CO ₂ H	СН3	осн з	СНЗ	COCH 3

СНЗ

OH

Н

EXAMPLE	A	R ³	R 5	E	Р
NO.				_	

EXAMPLE NO.	A	R ³	R ⁵	E	P

EXAMPLE NO.	A	R ³	R ⁵	E	P
•			A second		

EXAMPLE	A	R ³	R ⁵	E	P
NO.				- :	

$$C \equiv CH \quad CH_3 \quad H \quad H$$

EXAMPLE NO.	A	R ³	R ⁵	E	P	
303	H-Z	С≕СН	осн з	Н	СОСНЗ	
304	H Z H	С≡СН	OCH 3	СНЗ	Н	
305	N H	С≡СН	OCH 3	СН3	COCH 3	
306	H N N N N N N N N N N N N N N N N N N N	С≌СН	OH	н	н	
307	N I I	С≕СН	OH	Н	COCH 3	

EXAMPLE	A	R ³	R ⁵	· E	P .	\cdot
NO.			 			النب

EXAMPLE	A	R ³	R ⁵	E	P
NO.					

EXAMPLE NO.	A	R ³	R ⁵	E	Р
318	N H	C≡CH ₂	OCH 3	Н	н
319	N H	C≡CH ₂	OCH 3	H	сосн3
320	H N H	C≡CH ₂	OCH 3	СНЗ	н
321	N-H N-H	C≡CH ₂	OCH 3	СНЗ	COCH 3
322		C≡CH ₂	OH	н	н

EXAMPLE	A	R ³	R 5	E	P
NO.					

323
$$C = CH_2$$
 OH H COCH 3

$$C = CH_2$$
 OH CH_3 H

EXAMPLE NO.	A	R ³	R ⁵	E	P
328	HO N H	∕ C≡CH	OCH 3	СН3	Н
329	HO N	/ C≡CH	OCH 3	СН3	COCH 3
330	HO N	/ C≡CH	OН	Н	Н
331	HO N	/ C≡CH	OH	н	COCH 3
332	HO) C≡CH	OH	СН3	Н

EXAMPLE	A	R ³	R ⁵	E	P
NO.				•	

EXAMPLE	Δ	R 3	p 5	TP.	D.
NO.		••			-

EXAMPLE	A	R ³	R ⁵	F.	D
NO.					

EXAMPLE	A	R ³	R ⁵	E	P .
NO.					

EXAMPLE	A	. R ³	R 5	E	P
NO.					

EXAMPLE NO.	A	R ³	R ⁵	E	P
357	OH N I H	у н	ОН	СН3	соснз
358 `	THE PROPERTY OF THE PROPERTY O	н	ОСН 3	Н	Н
359	T N H	н	OCH 3	Н	COCH 3
360	I N H	н	OCH 3	СН3	H
361	- H	Н	OCH 3	СНЗ	COCH 3

EXAMPLE NO.	A	R ³	R ⁵	E	P
362	T-Z-H	Н .	OCH 3	н	Н
363	-H-H	Н	ОН	Н	COCH 3
364	H H	Н	ОН	Н	н
365	I-ZZ-I	н	OН	СН3	СОСН 3
366	Br N H	н	OCH 3	Н	н

EXAMPLE	Α	R ³	R 5	E	P
NO.					

EXAMPLE	Δ	ъ3	10 5	727	D
		21	EV -	2	
NO.					
I NO.					
			** **		

371 H OH H COCH 3

372 H OH CH3 H

373 H OH CH3 COCH3

374 H 0CH3 H H

375 H CCH₃ H COCH₃

EXAMPLE	A	R ³	R ⁵	E ·	P
NO.					

EXAMPLE	A	R ³	R ⁵ .	E	P
NO.					

OH

СН3 СОСН3

5

OCH 3

H H

10 383

OCH 3

н соснз

384

OCH 3

СН3 Н

15

385

OCH 3

снз сосыз

10

EXAMPLE	A	R ³	R ⁵	E	P
NO.					

386 CH_3 H CH H H

387 CH₃ H OH H COCH 3

СH₃ Н ОН СH₃ Н

15 389 CH₃ H OH CH₃ COCH₃

390 CH₃ CCH₃ H H

EXAMPLE	A	R ³	R ⁵	F.	D	
NO.					•	ı I

EXAMPLE NO.	A	R ³	R ⁵	E	P
395	H-K-H	СНЗ	OН	Н	COCH 3
396	LN-H	СН3	OH	Н	сосн 3
397	CYN-H	СН3	OH .	СН3	сосн3
398	С2Н	CH=CH2	СНЗ	Н	H
399	С2Н5	CH=CH2	OCH 3	н	сосн3
400	С2Н5	CH=CH2	OCH 3	CH3	Н
401	С2Н5	CH=CH ₂	· 0CH3	СНЗ	COCH 3
402	С2Н5	CH=CH2	OH	H	Н

147

EXAMPLE NO.	A	, R ³	R ⁵	E	P	
				d demonstrating of processing and pr		السيد
403	C2H5	CH=CH ₂	OH	н	COCH 3	
404	C2H5	CH=CH2	OH	н	COCH 3	
405	С2Н5	CH=CH ₂	ОH	СНЗ	COCH3	
406	C ₂ H ₅	C≒CH	OCH 3	H	н	
407	С ₂ н ₅	C≡CH	OCH 3	Н	сосн3	
408	С2Н5	C≔ CH	OCH 3	СН3	Н	
409	С2Н5	C≡CH	OCH 3	СНЗ	сосн з	
410	С2Н5	C≡ CH	ОН	Н	н	
411	С2Н5	C≡ CH	OH	н	COCH 3	

EXAMPLE NO.	A	R ³	R ⁵	E	P	
412	C2H5	C≡CH	ОН	H	COCH 3	*
413	C ₂ H ₅	C≡CH	OH	CH ₃	COCH3	

The following Examples #414-#461 of Table VI are highly preferred conjugates formed from tyrosine hydroxylase inhibitor compounds and glutamic acid derivatives. These tyrosine hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula III, above.

TABLE VI

EXAMPLE NO.	R ¹¹	R ³	_R 5	Е	Р
414	OН	Н	OH	Н	Н
415	ОH	Н	OH	Н	COCH ₃
416	OH	Н	OH	CH ₃	н
417	OH	Н	OH	CH ₃	COCH 3
418	OH	Н	OCH 3	H	Н
419	OH	Н	OCH 3	H	COCH 3
420	OH	Н	OCH 3	СН3	Н
421	OH	H ·	OCH 3	СН3	COCH 3
422	OH	СН3	OH	н	Н
423	OH	СН3	OH	Н	COCH 3
424	OH	CH ₃	OH	CH ₃	Н

EXAMPLE NO.	R11 .	_R 3	_R 5	E	P
425	OH	СН3	OH	CH ₃	COCH ₃
426	OH	CH3	OCH 3	н .	4
427	OH	CH ₃	OCH 3	Н	COCH 3
428	OH	CH3	OCH 3	CH ₃	H
429	OH	CH ₃	OCH 3	CH3	COCH 3
430	OH	Н	NH ₂	н .	н
431	OH	Н .	NH ₂	Н	COCH 3
432	OH	Ħ	NH ₂	CH3	н
433	OH	Н	NH ₂	CH3	COCH ₃
434	OH	СНЗ	NH ₂	Н .	H.
435	OH	CH ₃	NH ₂	Н	COCH3
436	OH	CH ₃	NH ₂	CH3	H
437	OH	CH ₃	NH ₂	CH ₃	COCH 3
438	OCH 3	Н	OH	Н	.н
439	OCH 3	н	OH	Н	COCH 3
440	OCH 3	Н	OH	CH3	Н
441	OCH 3	Н	OH	CH ₃	COCH 3

EXAMPLE	R ¹¹	R ³	_R 5	-	
NO.			R ⁻	E	P
442	OCH 3	Н	OCH 3	Н	н
443	OCH 3	н	OCH 3	Н	COCH ₃
444	OCH 3	Н	OCH 3	СН3	Н
445	OCH 3	н .	OCH 3	СН3	COCH 3
446	OCH 3	CH ₃	OH	Н	Н
447	OCH 3	CH ₃	OH	Н	СОСН3
448	. OCH 3	CH ₃	ОН	CH ₃	Н
449	OCH 3	СНЗ	OН	CH ₃	COCH 3
450	OCH 3	CH ₃	OCH 3	Н	Н
451	OCH 3	CH ₃	OCH 3	н	COCH 3
452	OCH 3	СНЗ	OCH 3	СН3	Н
453	OCH 3	CH ₃	OCH 3	СН3	COCH 3
454	OCH 3	Н	NH ₂	Н	Н
455	OCH 3	Н	NH ₂	н	COCH 3
456	OCH 3	H	NH ₂	CH ₃	Н
457	OCH 3	Н	NH ₂	CH ₃	COCH 3

152

EXAMPLE NO.	R ¹¹	R ³	R ⁵	E	P.
458	OCH 3	СНЗ	NH ₂	Н	Н .
459	OCH 3	СНЗ	NH ₂	Н	COCH 3
460	OCH 3	СН3	NH ₂	CH ₃	H
461	OCH 3	CH3	NH ₂	CH3	COCH 3

The following Examples #462-#857 comprise five classes of highly preferred conjugates composed of dopadecarboxylase inhibitor compounds and glutamic acid derivatives. Examples #462-#464 are descriptions of specific preparations of such conjugates. Examples #465-#857, as shown in Tables VII-XI, may be prepared by procedures shown in these specific examples and in the foregoing general synthetic procedures of Schemes 1-7.

10

Example 462

15

4-amino-4-carboxy-1-oxobutyl-3-hydroxy- α -methyl-L-tyrosine, methyl ester.

20 Step. 1: <u>Preparation of α-methyl-L-DOPA, methyl ester.</u> hydrochloride.

A suspension of 29.7 g (141 mmol) of α -methyl-L-DOPA in 300 mL of absolute methanol was cooled to -15°C and treated with 125.8 g (1.06 mol) thionyl chloride under a nitrogen atmosphere. The reaction was allowed to warm to ambient temperature and stir at reflux for 3 days. Concentration followed by trituration with ether gave 31.7g (97%) as an off-white solid: NMR (DMSO-d₆) δ 1.47 (s, 3H), 30 2.92 (d, \mathcal{J} = 12 Hz, 1H), 2.98 (d, \mathcal{J} = 12 Hz, 1H), 3.74 (s, 3H), 6.41 (d of d, \mathcal{J} = 9 Hz AND 2 Hz, 1H), 6.54 (d, \mathcal{J} = 2 Hz,

1H), 6.68 (d, J = 9 Hz, 1H), 8.46-8.90 (br s, 3H), 8.93 (s, 1H), 8.96 (s, 1H).

Step 2: <u>Preparation of 4-amino-4-carboxy-1-oxobutyl-3-bydroxy-α-methyl-L-tyrosine, methyl ester.</u>

Under nitrogen, a solution of 32.7 g (108 mmol) of N-Boc-L- γ -glutamic acid- α -t-butyl ester (BACHEM) in 150 mL of methylene chloride was treated with 11.14 g (54 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction was 10 allowed to stir for 2 hr prior to filtration under a nitrogen atmosphere. The methylene chloride was removed in vacuo and the residue dissolved in 110 mL of dimethylformamide (DMF). The anhydride solution was slowly added to a solution of 12.9 g (49 mmol) of the α -methyl-DOPA ester from step 1 and 12.6 g 15 (98 mmol) of diisopropylethylamine (DIEA) in 50 mL of anhydrous DMF. The reaction was allowed to stir overnight and was concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with 1N citric acid, 1N NaHCO3, water, and brine, dried (Na₂SO₄), and concentrated in vacuo to give 20 the protected coupled product; a solution of this material in 100 mL of methylene chloride was cooled to 0°C and treated with 400 mL of trifluoroacetic acid (TFA) under nitrogen. The reaction was allowed to warm to ambient temperature and stir for 72 hr. Concentration in vacuo gave 4-amino-4-25 $carboxy-1-oxobutyl-3-hydroxy-\alpha-methyl-L-tyrosine$, methyl ester: NMR (DMSO-d₆) δ 1.40 (s, 3H), 1.85-2.30 (m, 2H), 2.30-2.50 (m, 2H), 2.77 (d, J = 12 Hz, 1H), 3.00 (d, J = 12Hz, 1H), 3.58 (s, 3H), 3.85-4.10 (m, 1H), 6.29 (d of d, $\vec{I} = 9$ Hz and 2 Hz, 1H), 6.45 (d, \underline{J} = 2 Hz, 1H), 6.62 (d, \underline{J} = 9 Hz, 30 1H); MS (FAB) m/e (rel intensity) 355 (92), 225 (51), 148 (35).

Example 463

5 N-[4-(acetylamino)-4-carboxy-1-oxobuty1]-3-hydroxy- α -methyl-L-tyrosine, methyl ester.

The compound of Example 462 was dissolved in 100 ${\tt mL}$ of degassed water and under nitrogen the pH adjusted to 9 with 1 M K_2CO_3 . The solution was cooled to 0°C and 12 mL 10 (127 mmol) of acetic anhydride and 180 mL (180 mmol) of 1 M $\,$ ${\rm K}_2{\rm CO}_3$ was added every 30 min. for 5h; the pH was maintained at 9 and the reaction temperature kept below 5°C. After the last addition, the reaction was allowed to warm to ambient temperature overnight. The pH was adjusted to 3 with 3M HCl 15 and concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) using a 5-15% gradient of acetonitrile/water (0.05% TFA) gave 14.0g (49%) of colorless product: NMR (DMSO-d₆) δ 1.15 (s, 3H), 1.70-1.83 (m, 2H), 1.85 (s, 3H), 1.87-2.00 (m, 2H), 2.15 (t, \underline{J} = 7 Hz, 20 2H), 2.75 (d, $\underline{J} = 12 \text{ Hz}$, 1H), 3.00 (d, $\underline{J} = 12 \text{ Hz}$, 1H), 3.55 (s, 3H), 4.10-4.22 (m, 1H), 6.29 (d of d, J = 9 Hz and 2Hz, 1H), 6.43 (d, \underline{J} = 2Hz, 1H), 6.60 (d, \underline{J} = 9 Hz, 1H), 7.96 (s, 1H), 8.12 (d, \underline{J} = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 397 (100), 365 (10), 226 (70), 166 (90), 153 (22), 130 (72), 102 25 (28).

Example 464

N-[4-(acetylamino)-4-carboxy-1-oxobutyl]-3-hydroxy-α-methyl-L-tyrosine.

A solution of 13.5 g (102 mmol) of the compound of Example 463 in 34 mL of water was cooled to 0°C and treated with 102 mL (102 mmol) of 1N NaOH (all solutions were 10 degassed in vacuo and flushed with nitrogen prior to use). The reaction was stirred at ambient temperature for 5 hr and the pH adjusted to pH 1 with 6N HCl. Purification by reverse phase chromatography (Waters Deltaprep-3000) using a 2-10% gradient of acetonitrile/water (0.05% TFA) gave 8.9 g (68%) 15 of colorless product: NMR (DMSO-d₆) δ 1.18 (s, 3H), 1.70-1.83 (m, 2H), 1.85 (s, 3H), 1.87-2.00 (m, 2H), 2.15 (t, $\underline{J} = 7$ Hz, 2H), 2.75 (d, J = 12 Hz, 1H), 3.05 (d, J = 12 Hz, 1H), 4.10-4.23 (m, 1H), 6.31 (d of d, J = 9 Hz and 2 Hz, 1H), 6.47 $(d, \underline{J} = 2 \text{ Hz}, 1\text{H}), 6.60 (d, \underline{J} = 9 \text{ Hz}, 1\text{H}), 7.71 (s, 1\text{H}), 8.15$ 20 (d. J = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 383 (23), 212 (10), 166 (18), 130 (21), 115 (23); HRMS. Calcd for M + H: 383.1454. Found: 383.1450. Anal: Calcd for C₁₇H₂₂N₂O₈•1.06 H₂O•0.85 TFA: C, 48.67; H, 5.59; N, 6.46; F, 3.73. Found: C, 49.02; H, 5.73; N, 6.40; F, 3.70. 25

The following Examples #465-#541 of Table VII are highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. These dopa-decarboxylase inhibitors utilized to make these conjugates are embraced by generic Formula IV, above.

TABLE VII

EXAMPLE	2	R±	E.	P
	. **	. • •		1
NO.				
110.	· · · · · · · · · · · · · · · · · · ·			

EXAMPLE	· A	\mathbb{R}^{1}	E	P
NO.				

EXAMPLE NO.	A	R ¹	E	P
472	-N-CH ₂ OH	Н	СН3	Н
473	-N-CH ₂ -OH CH ₃	н	СНЗ	COCH 3
474	OH OH -CH ₂ OH	NH2	н	н
475	OH OH -CH ₂ OH	NH2·	Н	COCH 3
476	OH OH -CH ₂ OH	NH2	СН3	Н

EXAMPLE NO.	A	R ¹	E	P
477	OH OH -CH ₂ OH	NH2	СН3	COCH 3
478	CH ₃ OH -N-C-CH ₂ OH H GO ₂ H	Н	н	Н
479	CH ₃ OH -N-C-CH ₂ OH H CO ₂ H	Н	н	СОСН 3
480	CH ₃ OH -N-C-CH ₂ OH -N-C-CH ₂ OH H CO ₂ H	Н	СН3	н
481	CH₃ OH -N-C-CH₂ OH	н	СН3	COCH 3

i

EXAMPLE NO.	A	R ¹	E .	P
482	CH ₃ -C-CH ₂ -CO ₂ H	NH2	Н	H
483	CH ₃ -C-CH ₂ -CO ₂ H	NH2	Н	COCH 3
484	CH ₃ CC-CH ₂ OH CO ₂ H	NH2	СН3	Н
485	CH ₃ OH -C-CH ₂ OH CO ₂ H	NH2	СНЗ	COCH 3

EXAMPLE NO.	А	R ¹	E	P
4 86	CH ₂ F C-C-CH ₂ OH CO ₂ H	Н	н	Н
487	CH ₂ F -C-CH ₂ OH -C-CH ₂ OH -CO ₂ H	н	H	СОСН 3
488	CH ₂ F -C-CH ₂ OH 	н	СНЗ	Н

EXAMPLE NO.	A	R ¹	E	P
490	CHF ₂ OH -C-CH ₂ OH CO ₂ H	н	Н	H
491	CHF ₂ OH C-CH ₂ OH CO ₂ H	Н	Н .	COCH 3
492	CHF ₂ OH C-CH ₂ OH CO ₂ H	Н	СН3	H
493	CHF ₂ OH -C-CH ₂ OH CO ₂ H	H	СН3	сосн.з

EXAMPLE	A	\mathbb{R}^1	E	P
NO.				

EXAMPLE NO.	A	R ¹	E	Þ
498	CH ₃ OH -C-CH ₂ OH -CO ₂ CH ₃	NH2	н	н
499	CH ₃ OH -C-CH ₂ OH CO ₂ CH ₃	NH2	Н	COCH 3
500	CH ₃ CC-CH ₂ OH CO ₂ CH ₃	NH2	СНЗ	Н
501	CH ₃ C-CH ₂ OH CO ₂ CH ₃	NH2	СНЗ	COCH 3

EXAMPLE NO.	A	R ¹	E	P
502	CH ₂ F -C-CH ₂ OH 	Н	Н	H
503	CH ₂ F -C-CH ₂ OH -CO ₂ CH ₃	Н	Н	COCH 3
504	CH ₂ F -C-CH ₂ OH 	н	CH3	Н
505	CH ₂ F -C-CH ₂ OH CO ₂ CH ₃	н	СНЗ	СОСН 3

EXAMPLE NO.	Α .	R ¹	E	P
506 _.	CHF ₂ OH -C-CH ₂ OH CO ₂ CH ₃	н	н .	H
507	CHF ₂ OH -C-CH ₂ OH CO ₂ CH ₃	Н	Н	COCH 3
508	CHF ₂ OH -C-CH ₂ OH CO ₂ CH ₃	н	СНЗ	H
509	CHF ₂ OH -C-CH ₂ OH CO ₂ CH ₃	Н	СН3	COCH 3

EXAMPLE NO.	A	R ¹	E	Р
510	CH ₃ OH -C-CH ₂ OH CO ₂ CH ₃	Н	H	н
511	CH ₃ OH -C-CH ₂ OH CO ₂ CH ₃	н	Н	сосн з
512	CH ₃ OH -C-CH ₂ OH CO ₂ CH ₃	н	СНЗ	Н
513	CH ₃ OH -C-CH ₂ OH CO ₂ CH ₃	Н	СНЗ	COCH 3

EXAMPLE NO.	A	R ¹	E	P
514	CH ₃ OH -C-CH ₂ OH CO ₂ CH ₃	H	Н	Н
515	CH ₃ C-CH ₂ OH CO ₂ H	Н	H	COCH 3
516	CH ₃ OH -C-CH ₂ OH CO ₂ H	н	СНЗ	H
517	CH ₃ OH -C-CH ₂ OH CO ₂ H	Н	СН3	COCH 3

EXAMPLE NO.	A	R ¹	E	P
518	CF ₃ C-C-CH ₂ OH CO ₂ CH ₃	H	н	Н
519	CF ₃ -C-CH ₂ -C-CH ₂ -CO ₂ CH ₃	н	Н	. СОСН 3
520	CF ₃ OH -C-CH ₂ OH CO ₂ CH ₃	н	СНЗ	н

EXAMPLE NO.	A	R ¹	E	P
522	CF ₃ C-C-CH ₂ OH CO ₂ H	н	н .	Ĥ
523	CF ₃ OH -C-CH ₂ OH CO ₂ H	н	Н	соснз
524	CF ₃ -C-CH ₂ CO ₂ H	H	СН3	H
525	CF ₃ -C-CH ₂ OH -CO ₂ H	н	СН3	COCH 3

EXAMPLE NO.	A	R ¹	E	P
526	C ₂ H ₅ OH -C-CH ₂ OH CO ₂ CH ₃	н	Н	Н
527	C ₂ H ₅ OH -C-CH ₂ OH CO ₂ CH ₃	н	Н	COCH 3
528	C ₂ H ₅ OH -C-CH ₂ OH CO ₂ CH ₃	н	СНЗ	н
529	C_2H_5 OH C_2CH_2 OH CO_2CH_3	н	СНЗ	СОСН 3

EXAMPLE NO.	A	R ¹	E	P
530	C_2H_5 OH C_2CH_2 OH CO_2CH	H	н	H
531	C ₂ H ₅ OH -C-CH ₂ OH CO ₂ H	H .	н	сосн 3
532	C ₂ H ₅ OH -C-CH ₂ OH CO ₂ H	н	СН3	н
533	C ₂ H ₅ OH -C-CH ₂ OH CO ₂ H	H _.	СН3	COCH 3

EXAMPLE NO.	A.	R ¹	E	P
NO.		 		

EXAMPLE NO.	A	R ¹	E	P
538	C ₃ H ₇ -C-CH ₂ 	Н	н	H
539	C ₃ H ₇ OH -C-CH ₂ OH CO ₂ H	Н	Н	COCH 3
540	С ₃ Н ₇ -C-CH ₂ -ОН СО ₂ Н	H	СН3	H
541	C ₃ H ₇ OH -C-CH ₂ OH CO ₂ H	н	СН3	COCH 3

The following Examples #542-#577 of Table VIII are highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. These dopa-decarboxylase inhibitors utilized to make these conjugates are embraced by generic Formula VIII, above.

10

TABLE VIII

EXAMPLE	L	М	_{. R} 56	_R 55	E	P
NO.				 		

EXAMPLE	L	М	_R 56	_R 55	F.	p
NO.						

545	NHNH	ОН	Ή	Н	СНЗ	COCH 3
546	NHNH	-C OCH3	Br	н	н	Н
547	NHNH	°C → OCH3	Br	н	Н	COCH 3
548	NHNH	OCH₃	Br	н	СН3	Н
		O OCH₃				

EXAMPLE	L	М	_R 56	_R 55	E	P (
NO.			·			

551 NHNH -CH
$$C_2H_5$$
 Br Br H COCH 3

552 NHNH
$$-CH + C_2H_5$$
 Br CH3 H

553 NHNH -CH
$$C_2H_5$$
 Br Br CH3 COCH 3

EXAMPLE	L	М	_R 56	_R 55	E	P
NO.			• •	• •		- 1

EXAMPLE	L	M	_R 56	_R 55	E	P
NO.		•				

EXAMPLE	L	M	p.56	_R 55	777	
i i	- .	1.1	K	KOO	Ľ	P
NO.						

		<u> </u>				
TYNDIE	T	M	_R 56	_R 55	· E	Р
EXAMPLE		11	• •	• •		- ,
NO.						

piperazinyl -CH
$$C_2H_5$$
 Br Br H H

EXAMPLE	L	М	_R 56	_R 55	E	P
NO.						

piperazinyl -CH
$$\left\{\begin{array}{cccc} C_2H_5\\ \end{array}\right\}_2$$
Br Br CH3 H

piperazinyl -CH
$$\left\{\begin{array}{cccc} C_2H_5 \\ 2\end{array}\right\}_2$$
 Br CH3 COCH3

The following Examples #578-#757 of Table IX are highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. These dopa-decarboxylase inhibitors utilized to make these conjugates are benzoic acid type derivatives based on the list of similar compounds described earlier.

TABLE IX

EXAMPLE NO.	L	R130	_R 131	_R 132	E	P
578	NHNH	Н	OH	ОН	Н	Н
579	NHNH	н	OH	ОН	Н	сосн 3
580	NHNH	H	OH	OH	СНЗ	H
581	NHNH	н	OH	OH	СНЗ	COCH 3
582	NHNH		ОН	ОН	Н	Н
583	NHNH		OH	ОН	н	сосн з
584	NHNH		OH	ОН	СН3	Н

EXAMPLE NO.	L	_R 130	R ¹³¹	_R 132	E	P
585	NHNH		ΟΉ	ОН	СН3	COCH ₃
586	NHNH	——————————————————————————————————————	OH	ОН	H ·	H
587	NHNH	c	OH	ОН	Н .	COCH 3
588	NHNH	c	OH	OH	СНЗ	Н
5 <u>8</u> 9	NHNH	c	: I OH :	OH	СНЗ	COCH 3
590	NHNH	OCH ₃ OCH	OCH 3	OCH 3	H	H
591	NHNH	OCH OCI	OCH ₃	OCH 3	н	COCH 3

		-	
	——OCH ₃	————осн ₃	————och₃

EXAMPLE NO.	L	_R 130	R131	R132 E	P
599	NHNH	OCH ₃	H ₃ OCH 3	осн з н	COCH 3
600	NHNH	OCH3	H ₃ OCH 3	OCH 3 CH3	H
601	ИНИН	OCH3	H₃ OCH 3	OCH 3 CH3	COCH 3
602	NHNH		OCH 3	осн з н	H
603	NHNH		OCH 3	осн з н	сосн 3
604	NHNH		OCH 3	OCH 3 CH3	H
605	NHNH		OCH 3	OCH 3 CH3	COCH 3
606	NHNH		H OH	ОН Н	H

EXAMPLE NO.	L	_R 130	R131	_R 132	E	P
					= wu	
607	NHNH	— ОН	OH	OH	H	COCH 3
608	NHNH	— ОН	OH	ОН	СНЗ	Н
609	NHNH	———он	OH	OH	СНЗ	сосн з
610	NHNH	—CI	0CH 3	OCH 3	Н	Н
611	NHNH	—CI	OCH 3	OCH 3	Н	COCH 3
612	NHNH	—CI	0СН3	0СН 3	СН3	н
613	NHNH	—CI	0СН3	OCH 3	СНЗ	COCH 3
614	NHNH	OCH3	OCH 3	0СН 3	Н	Н

EXAMPLE NO.	L	R130	_R 131	R132	E	P
615	NHNH		CH ₃ OCH 3	OCH 3	H	COCH 3
616	NHNH		CH ₃ OCH 3	OCH 3	СНЗ	H
617	NHNH		CH _{3 OCH 3}	OCH 3	СНЗ	COCH 3
618	NHNH	-\CH		OCH 3	Н	Н
619	NHNH	-CH	.~.	OCH 3	H	сосн з
620	NHNH	N CH	0077	OCH 3	СНЗ	H
621	NHNH ·	-CH	001.5	OCH 3	СН3	COCH 3
622	NHNH		OН	OH	н	H

EXAMPLE NO.	L	R130	R ¹³¹	R132	E	P
623	NHNH		ОН	ОН	н	COCH 3
624	NHNH		OH	ОН	СНЗ	Н
625	NHNH		ОН	ОН	СНЗ	COCH 3
626	NHNH		OCH 3	OCH 3	Н	Н
627	NHNH		OCH 3	OCH 3	н	COCH 3
628	NHNH		OCH 3	OCH 3	СН3	н
629	NHNH		OCH 3	OCH 3	СНЗ	COCH 3
630	NHNH	~s	OCH 3	OCH 3	н	Н
631	NHNH	S	осн 3	осн з	Н	сосн 3

R132

R131

EXAMPLE NO. L

R130

					,	
632	NHNH	s	OCH 3	OCH 3	СН3	H (
633 .	NHNH		OCH 3	OCH 3	СНЗ	COCH 3
634	NHNH		OH	OH	Н	H
635	NHNH	$ \left(\begin{array}{c} s \\ \end{array} \right)$	OH .	OH	H	COCH 3
636	NHNH		OH	ОН	СН3	н
637	NHNH		OH	ОН	СН3	COCH 3
638	NHCH2CH2NH	Н	OH	OH	Н	H
639	NHCH 2 CH2 NH	H	ОН	OH	Н .	COCH 3
640	NHCH 2 CH2 NH	Н	OH	OH .	СНЗ	н
641	NHCH 2 CH2 NH	Н	OH	OH	СНЗ	COCH 3

EXAMPLE NO.	L	_R 130	R131	_R 132	E	₽.
642	NHCH 2 CH2 NH		OH	ОН	H	Н
643	NHCH 2CH2NH		OH	ОН	Н	COCH 3
644	NHCH 2CH2NH		OН	ОН	СНЗ	Н
645	NHCH 2 CH2 NH		OН	ОН	СН3	COCH 3
646	NHCH 2CH2NH	CI	ОН	ОН	Н	н
647	NHCH 2CH2NH	-CI	OH	ОН	Н	COCH 3
648	NHCH 2 CH2 NH	-CI	OH	ОН	СНЗ	н
649	NHCH 2 CH2 NH	-Ci	ОН	ОН	СН3	COCH 3

EXAMPLE	L	R130	R131	R132 E	P .
NO.					

6 50'	NHCH 2CH2NH	OCH3 OCH3	OCH 3	оснз н	H
651	NHCH 2CH2NH	OCH ₃		осн з н	сосн 3
652	NHCH 2CH2NH	OCH ₃ OCH ₃	CH.3	осн з снз	H
653	NHCH 2 CH2 NH	OCH ₃	OCH 3	OCH 3 CH3	COCH 3
654	NHCH 2CH2NH	- N	OCH 3	осн з н	H
655	NHCH 2CH2NH	—√N	OCH 3	осн з н	COCH 3
656	NHCH 2CH2NH	N N	OCH 3	осн з снз	H

EXAMPLE NO.	L	R130	R ¹³¹	R132 E	P
657	NHCH 2CH2NH	N	OCH 3	ОСН 3 СН3	COCH 3
658	NHCH 2CH2NH	OCH	OCH 3	осн з н	н
659	NHCH2CH2NH	OCH	осн _з осн _з Із	оснз н	сосн 3
660	NHCH 2 CH2 NH	ОСН	CH₃ OCH3	осн з снз	Н
661	NHCH 2 CH2 NH	ОСН	CH ₃ OCH 3	осн з снз	COCH 3
662	NHCH 2CH2NH		OCH 3	осн з н	Н
663	NHCH 2 CH2 NH		OCH 3	осн з н	COCH 3

EXAMPLE NO.	L	_R 130	R131	R132	E	P
664	NHCH 2CH2NH	─	OCH 3	OCH 3	СН3	н
			•			
665 ·	NHCH 2 CH2 NH		OCH 3	OCH 3	СНЗ	COCH 3
					· .	
666	NHCH 2 CH2 NH		H OH	OH	Н	H
667	NHCH 2CH2NH		H OH	OH ·	H.	COCH 3
607	Mich Zenzien		. 	011	**	300.3
668	NHCH 2 CH2 NH	-()-oı	H OH	OH	СНЗ	H
					· .	
669	NHCH 2 CH2 NH	—(H OH	OH	СНЗ	COCH 3
			·			
670	NHCH 2CH2NH		OCH 3	OCH 3	H	H
	۰					
671	NHCH 2 CH2 NH		OCH 3	OCH 3	H	COCH 3
			N	·		
672	NHCH 2 CH2 NH		, OCH 3	OCH 3	СНЗ	H

EXAMPLE	L	_R 130	_R 131	_R 132	r	D
NO.				•	E	-

673	NHCH 2 CH2 NH	CI OCH 3	осн 3 сн3	COCH 3
674	NHCH 2 CH2 NH	—CCH3 CCH3	оснз н	Н
675	NHCH 2 CH2 NH	OCH3 OCH3	осн з н	СОСН 3
676	NHCH 2CH2NH	OCH3 OCH3	осн з снз	Н
677	NHCH 2 CH2 NH	OCH3 OCH3	осн з снз	COCH 3
678	NHCH 2CH2NH	CH3 CCH3	осн з н	н
679	NHCH 2 CH2 NH	CH3 CCH3	осн з н	COCH 3
680	NHCH2CH2NH	CH ₃ OCH 3	осн з снз	Н

EXAMPLE NO.	L	R130	R131	R132	E	P
		N	CH₃			
681	NHCH 2 CH2 NH		CH3 OCH3	OCH 3	СН3	COCH3.
682	NHCH 2 CH2 NH		OH	OH .	H ·	H
683	NHCH 2CH2NH		OH	OH	Н	COCH 3
684	NHCH 2CH2NH		OH	OH ·	СНЗ	H
685	NHCH 2CH2NH		OH	ОН	СН3	COCH 3
686	NHCH 2CH2NH		OCH 3	OCH 3	Н	H
687	NHCH 2 CH2 NH		OCH 3	OCH 3	H	COCH-3
688	NHCH 2CH2NH		OCH 3	OCH 3	СНЗ	H
689	NHCH 2 CH2 NH		OCH 3	OCH 3	СН3	COCH 3

R¹³² E P

R131

R130

L

NO.	L	R130	R131	R13	2 E	P
690	NHCH 2 CH2 NH	s	OCH 3	ОСН	3 H	Н
691	NHCH 2CH2NH	S S	OCH 3	OCH :	3 Н	COCH 3
692	NHCH 2 CH2 NH		OCH 3	OCH (з СН3	Н
693	NHCH 2CH2NH	s	OCH 3	OCH 3	снз	COCH 3
694	NHCH 2CH2NH	$ \langle s \rangle$	ОН	OH	Н	Н
695	NHCH 2 CH2 NH	S	ОН	ОН	Н	COCH 3
696	NHCH 2 CH2 NH	~\s\	OH	ОН	СНЗ	н
697	NHCH2CH2NH	~s>	ОН	ОН	СНЗ	COCH 3
698	piperazinyl	Н	OH	OH	н	н

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EXAMPLE NO.	L	R130	_R 131	R132	E	P
. 699	piperazinyl	Н	OH	ОН	Н	COCH 3
700	piperazinyl	Н	OH	ОН	СНЗ	Ħ
701	piperazinyl	. н	OH	OH	СН3	COCH 3
702	piperazinyl		OH	ОН	Н	H C
703	piperazinyl		. OH	ОН	Н	COCH 3
704	piperazinyl		OH	ОН	СН3	H
705	piperazinyl		OH	ОН	CH ₃	сосн 3
706	piperazinyl		CI OH	OH	H .	н
707	piperazinyl		CI OH	ОН	Н	COCH 3

EXAMPLI NO.	E L	R130	R131	R132	E P
708	piperaziny.		-CI OH	. ОН С	ł3 н
709	piperazinyl		·CI OH	ОН СН	3 COCH 3
710	piperazinyl	OCH ₃	OCH ₃ CH ₃	оснз н	н
711	piperazinyl	OCH OCH	OCH ₃	оснз н	СОСН 3
712	piperazinyl	OCH3 OCH	OCH ₃	осн з снз	н
713	piperazinyl	\\ //	CH ₃ OCH 3	осн з снз	COCH 3
714	piperazinyl	—√∑N	OCH 3	оснз н	Н

EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R132	E	2
715	piperazinyl	-__N	OCH 3	OCH 3	н	COCH 3
716	piperazinyl	─	0CH3	осн 3	СН3	H
717	piperazinyl	— N	OCH 3	0СН 3	СН3	COCH 3
718	piperazinyl		-OCH ₃ CCH ₃	OCH 3	Н	Н
719	piperazinyl		-OCH ₃ OCH ₃ CH ₃	OCH 3	Н	COCH 3
720	piperazinyl		-OCH ₃ OCH ₃ CH ₃	OCH 3	СНЗ	1
721	piperazinyl		-OCH ₃ OCH ₃ CH ₃	OCH 3	СНЗ	COCH 3

EXAMPLE NO.	L .	R130	R131	_R 132	E	P
722	piperazinyl		OCH 3	OCH (3 H	Н
723	piperazinyl		OCH 3	OCH 3	3 Н	сосн 3
724	piperazinyl		OCH 3	OCH 3	сн3	Н
725	piperazinyl		OCH 3	OCH 3	СНЗ	COCH 3
726	piperazinyl	————он	OН	ОН	Н	Н
727	piperazinyl	————он	ОН	ОН	Н	COCH 3
728	piperazinyl	————ОН	OН	ОН	СНЗ	Н
729	piperazinyl	ОН	OΉ	ОН	СНЗ	сосн 3
730	piperazinyl	-CI	OCH 3	OCH 3	н	Н

EXAMPLE NO.	L	_R 130	_R 131	R132	E	P
731	piperazinyl	()-c	OCH 3	OCH 3	Н	COCH 3
732	piperazinyl	c	OCH3	OCH 3	Снз	H - 1867
732	processing			ours	 .	
733	piperazinyl	— <u> </u>	OCH 3	OCH 3	СНЗ	сосн 3
734	piperazinyl	—————OCH3	OCH 3	OCH 3	H	H
735	piperazinyl	————och³	OCH 3	OCH 3	Н	COCH 3
736	piperazinyl	OCH ₃	OCH 3	OCH 3	СНЗ	H
737	piperazinyl	OCH3	OCH 3	OCH 3	СН3	COCH 3
738	piperazinyl	—	H₃	OCH 3	H	・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・ ・

EXAMPLE NO.	L	R130	_R 131	_R 132	E	P
	*		CH₃			
739	piperazinyl		CH ₃ OCH 3	OCH (3 Н	COCH 3
740	piperazinyl	—	CH3 OCH3	OCH 3	з СН3	H
741	piperazinyl		CH³ ŒH3	OCH 3	СН3	COCH 3
742	piperazinyl		OΗ	ОН	Н	н
743	piperazinyl		ОН	ОН	н	COCH 3
744	piperazinyl		OH	ОН	СНЗ	Н
745	piperazinyl		OH	ОН	СНЗ	COCH 3
746	piperazinyl		OCH 3	OCH 3	Н	Н

EXAMPLE NO.	L	R130	R131	R132	E	P
747	piperazinyl		OCH 3	OCH 3	Н	COCH3
748	piperazinyl		OCH 3	OCH3	СНЗ	H
749	piperazinyl		OCH 3	OCH 3	СНЗ	COCH 3
750	piperazinyl	~\s\	OCH 3	осн 3	н	Н
751	piperazinyl		OCH 3	OCH 3	Н	COCH 3
752	piperazinyl	~s	OCH 3	осн з	СНЗ	H
753	piperazinyl	$ \langle s \rangle$	OCH 3	OCH 3	СНЗ	COCH'3
754	piperazinyl	-\s\sqrt{s}	ÓН	OH	н	Н
755	piperazinyl	~s	OH	OH	Н	COCH 3

EXAMPLE	L	_R 130	_R 131	R132	E	P
NO.						

756	piperazinyl		OH	ОН	СНЗ	Н
757	piperazinyl	¬\(\sigma\)	ОН	ОН	СН3	сосн 3

The following Examples #758-#809 of Table X are highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. These dopa-decarboxylase inhibitors utilized to make these conjugates are propenoic acid derivatives based on the list of similar compounds described earlier.

TABLE X

EXAMPLE NO.	R133	R ¹³⁴	R ¹³⁵	E	Р
758	н	~s	Н	н	Н
759	Н	¬{s}	H	н	COCH 3
76 0	н .	~\s\	Н	CH ₃	H
761	н	\$\rightarrow\s^{\mathbb{S}}	н	CH3	COCH 3
762	Сн3	~\s\	н	H	Н

EXAMPLE NO.	R133	R134	R ¹³⁵	E	P
763	СН3	~\s\	Н	Н	COCH ₃
764	СНЗ	~\s\	н	СН3	н
765	СН3	$ \langle s \rangle$	н	СН3	сосн з
766	Н	~s	CH3	Н	Н
767	н	s	CH ₃	н	COCH 3
768	Н	~s	СН3	Сн3	н
769	Н	s	CH3	CH ₃	COCH 3
770	н		Н	н	Н

EXAMPLE NO.	R133	R134	_R 135	E	P
771	Н		H	Н	COCH 3
772	н		Н	CH ₃	H (
773	н		Н	CH3	COCH 3
774	СН3		Н	н	H
775	СН3		H .	H	сосн з
776	СН3	~°>	Н	CH ₃	H
777	СН3	$\overline{}$	Н	СН3	COCH 3

EXAMPLE NO.	R133	R134	_R 135	E	P
778	н	s	Н	Н	н
779	н	s	н	н	COCH 3
780	H	$\int_{-\infty}^{\infty}$	н	CH ₃	Н
781	Н	s	н	СН3	COCH ₃
782	СН3	s s	н	н	н
783	СНЗ	<u></u> s	н	Н	COCH 3
784	CH ₃		Н	CH ₃	Н

		400			
EXAMPLE NO.	R133	R ¹³⁴	_R 135	E	P
785	СН3	s	н	CH3	COCH3
786	Н		Н	н	H .
7 87 .	H		Н	Н .	COCH 3
788	н		Н	CH3	H
789	Н		н .	СН3	COCH 3
790	СН3		Н	Н	H
791	СН3		: H	Н	COCH 3

EXAMPLE NO.	_R 133	R134	_R 135	E	P
792	СН3		н	СН3	Н
793	CH ₃		Н	CH ₃	сосн 3
794	Н		CH ₃	н	Н
795	Н		СНЗ	н	COCH 3
796	н		CH ₃	СН3	Н
797	н		СН3	CH3	сосн 3
798	Н		Н	Н	Н

		•			
EXAMPLE NO.	R133	_R 134	R135	E	P
799	Н		Н	Н	COCH 3
800	Н		Н	СН3	н
801	H		Н	СH3	COCH 3
802	СН ₃		н	н	H
803	СНЗ		н	Н	COCH 3
804	СН3		H . :	CH ₃	н
805	CH ₃		H :	СН3	COCH 3

EXAMPLE NO.	_R 133	_R 134	R135	E	P
806	н		СН3	Н	Н
807	Н		CH ₃	н	COCH ₃
808	н		CH3	CH3	н
809	н		CH ₃	CH ₃	COCH 3

The following Examples #810-#833 of Table XI are highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. These dopa-decarboxylase inhibitors utilized to make these conjugates are embraced by generic Formula IX, above.

TABLE XI

EXAMPLE NO.	R67	_R 136	E	P
810	H	Н	H	Н
811	Н	Н	Н	COCH 3
812	н	Н	СНЗ	Н
813	H	н	СН3	COCH 3
814	н	OH .	Н	H
815	Н	OH	Н	COCH 3
816	н	OH .	СНЗ	Н
817	н	OH ·	CH3	COCH 3
818	Н	OCH 3	Н	Н
819	н	OCH 3	Н	COCH 3
820	H	OCH 3	СНЗ	H
821	н	OCH 3	СНЗ	COCH 3
822	СНЗ	н	Н	н

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EXAMPLE NO.	_R 67	_R 136	. E	P
823	CH3	н	Н	COCH 3
824	СНЗ	Н	CH ₃	Н
825	СНЗ	н	СНЗ	COCH 3
826	СНЗ	OH	Н	Н
827	CH3	OH	Н	COCH 3
828	СНЗ	OH	СНЗ	Н
829	CH3	ОН	СНЗ	COCH 3
830	СНЗ	OCH 3	Н	н
831	Сн3	OCH 3	Н	COCH 3
832	СНЗ	OCH 3	CH3	Н
833	СНЗ	OCH 3	СНЗ	COCH 3

The following Examples #834-#857 of Table XII are highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. These dopa-decarboxylase inhibitors utilized to make these conjugates are embraced by generic Formula IX, above.

TABLE XII

P .	p.	E	_R 67	R139	_R 138	EXAMPLE NO.
	Н	н	C≡CH	Н	н	834
СН 3	COCH	Н	C≡CH	Н	н	835
	н .	СНЗ	C≡Œ	Н	Н	836
СНЗ	COCH	СНЗ	C≡CH	Н	Н	837
	H .	Н	C≡CH	н	OH	838
СНЗ	СОСН	н	C≡CH	н	OH .	839
	Н	СНЗ	C≡CH	Н	OH	840
СНЗ	COCH	СНЗ	C≡CH	Н	OH	841
	н	Н	C≡CH	OH	Н	842
СНЗ	СОСН	Н	C≡CH	OH	н	843
	H	СН3	C≡CH	OH .	н	844

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					•	
EXAMPLE NO.	R138	_R 139	_R 67	E	P	
845	Н	OН	С≡СН	СНЗ	СОСН 3	
846	Н	Н	CH=CH ₂	н	Н	
847	н	н	CH=CH ₂	н	COCH 3	
848	Н	Н	CH=CH ₂	СНЗ	Н	
849	Н	Н	CH=CH ₂	СНЗ	COCH 3	
850	OH	Н	CH=CH ₂	н	Н	
851	OH	. Н	CH=CH ₂	Н	COCH 3	
852	OH	Н	CH=CH ₂	CH ₃	н	
853	OН	Н	CH=CH ₂	СНЗ	COCH 3	
854	Н	OH	CH=CH ₂	Н	Н	
855	H	OH	CH=CH ₂	Н	COCH 3	
856	H	ОH	CH=CH ₂	CH3	Н	
857	Н	OH	CH=CH ₂	СНЗ	COCH 3	

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The following Examples #858-#1857 comprise five classes of highly preferred conjugates composed of dopamine- β -hydroxylase inhibitor compounds and glutamic acid derivatives. Examples #858-#863 are descriptions of specific preparations of such conjugates. Examples #864-#1857, as shown in Tables XIII-XVII, may be prepared by procedures shown in these specific examples and in the foregoing general synthetic procedures of Schemes 1-7.

Example 858

L-glutamic acid, 5-{[(5-butyl-2-pyridinyl)carbonyl]hydrazide}

Step. 1: <u>Preparation of 5-n-Butylpicolinic (Fusaric) Acid</u>
<u>Hydrazide</u>.

A solution of 36.0 g (0.20 mol) of fusaric acid (Sigma) in 800 ml of absolute methanol was cooled to -10°C by means of an ice/methanol bath and 120 ml (199 g, 1.67 mol) of SOC1 2 was added dropwise over a 1 hr period. The reaction was allowed to slowly warm to ambient temperature and then stirred at reflux for 72 hr. The reaction was concentrated; the addition of 100 ml of toluene (twice) followed by reconcentration insured the complete removal of any unreacted SOC12. The viscous syrup thus formed was dried in vacuo (0.01mm) overnight prior to treatment with cold NaHCO3 (sat). The ester was extracted with ether and dried (MgSO₄). Concentration gave 32.3 g (83%) of crude methyl fusarate which was redissolved in 100 ml of absolute methanol and cooled to 0°C. Under a nitrogen atmosphere, 5.5 ml (0.174 mol) of anhydrous hydrazine was slowly added by syringe. The reaction: was allowed to slowly warm to ambient temperature and stir

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overnight. The methanol was removed and the yellow-brown residue was dried in <u>vacuo</u> (0.01 mm) overnight where it solidified producing 31.7g (98%) based on ester) of crude hydrazide. Recrystallization from ether/hexane gave colorless needles: mp 51-53°C NMR (CDC1₃) δ 0.95 (t, \underline{J} = 7 Hz, 3H, CH₂CH₃); 1.30-1.45 (m, 2H, CH₂CH₃); 1.55-1.70 (m, 2H, CH₂CH₂CH₂); 2.67 (t, \underline{J} = 7 Hz, 2H, ArCH₂); 7.65 (d of d, \underline{J}_3 , \underline{J}_4 = 7 Hz and \underline{J}_4 , $\underline{\delta}_5$ = 2 Hz, 1H, ArH); 8.05 (d, \underline{J}_3 , \underline{J}_4 = 7 Hz, 1H, ArH); 8.37 (d, 1H, ArH, \underline{J}_4 , $\underline{\delta}_5$ = 2 Hz); HRMS. Calcd for M + H: 194.1270. Found: 194.1293.

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Step 2: <u>Preparation of L-glutamic acid</u>, 5-{[(5-butyl-2-pyridinyl)carbonyl]hydrazide}.

A solution of 7.27 g (24.0 mmol) of Boc-L-yglutamic $acid-\alpha-t$ -butyl ester (BACHEM) in 150 ml of anhydrous THF was 15 cooled to 0°C under static nitrogen and treated with 2.7 ml (2.46 g, 24.4 mmol) of anhydrous N-methyl morpholine. The mixture was then slowly treated with 3.1 ml (3.26 g, 23.9 mmol) of isobutyl chloroformate and allowed to stir for 1 hr prior to the dropwise 20 addition of a solution of 3.86 g (20.0 mmol) of fusaric acid hydrazide from step 1 in 30 ml of anhydrous THF. The reaction mixture was stirred at 0°C for 2 hr and then allowed to warm to ambient temperature and stir overnight. The N-methylmorpholine hydrochloride was removed by filtration and the filtrate concentrated in vacuo to give 11.5 g of crude product which was a 25 colorless glass. This material was dissolved in 50 ml of $\mathrm{CH_{2}Cl_{2}}$ and treated with 50 ml of CF3CO2H. After 4 hr at ambient temperataure, the volitiles were removed in vacuo. The addition of acetonitrile caused the product to precipitate producing 3.97 g (46%) of colorless material: mp 162-164°C (dec.); NMR (DMSO-30 d₆) δ 1.90 (t, J = 7 Hz, 3H, CH₂CH₃); 1.30-1.45 (m, 2H, CH₂CH₃); 1.50-1.65 (m, 2H, $CH_2CH_2CH_2$); 2.00-2.20 (m, 1H, CH_2CH); 2.30-2.50 (m, 1H, CH₂CH); 2.70 (t, J = 7 Hz, 2H, ArCH₂); 3.60 (t, J = 7 Hz, 2H, $COCH_2$); 3.95-4.05 (M, 1H, CH_2CH); 7.85 (d of d, $J_{3,4} = 7 Hz$

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and $\underline{J}_{4,6} = 2$ Hz, 1H, ArH); 7.95 (d, $\underline{J}_{3,4} = 7$ Hz, 1H, ArH); 8.55 (d, $\underline{J}_{4,6} = 2$ Hz, 1H, ArH).

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Example 859

N-acetyl-L-glutamic acid, 5-[(5-butyl-2-pyridinyl)-carbonyllhydrazide

A suspension of 2.85 g (6.54 mmol) of the compound of Example 858 in CH₃CN/H₂O (1:1) was treated with 2 equiv. of 1 M 15 K₂CO₃ at 0°C. With efficient stirring, 1 ml (10.6 mmol) of acetic anhydride and 11 ml (11 mmol) of 1M K2CO3 were added every 10 min for 1 hr; since the product is soluble, the mixture became homogenous as the reaction proceeded. The reaction mixture was stirred for 1 hr, filtered, and the filtrate cooled to 0°C. The pH was adjusted to pH 4 by the careful addition of cold dilute 20 HC1. All volitiles were removed in vacuo and the product dissolved in ethanol. Recrystallization from ethanol/petroleum ether produced 2.16g (69%) of colorless material: mp 191.5-192.0°C; NMR (D₂O and NaOD) δ 0.85 (t, $\underline{J} = 7$ Hz, 3H, CH₂CH₃); 25 1.20-1.35 (m, 2H, CH_2CH_3); 1.55-1.70 (m, 2H, $CH_2CH_2CH_2$); 1.95-2.10 (m, 1H, CH_2CH); 2.05 (s, 3H, $COCH_3$); 2.20-2.35 (m, 1H, CH_2CH); 2.45 (t, J = 7 Hz, 2H, $COCH_2$); 2.75 (t, 2H, $ArCH_2$); 3.45-3.55 (m, 1H, CH₂CH); 8.05 (s, 2H, ArH); 8.55 (s, 1H, ArH); HRMS. Calcd for M + H: 365.1825. Found 365.1860.

Anal. Calcd. for $C_{17}H_{24}N_4O_5$: C, 55.98; H, 6.58; N, 15.36. Found: C, 55.96; H, 6.64; N, 15.30.

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Example 860

N-[2-[[(5-butyl-2-pyridinyl)carbonyl]amino]ethyl]-L-glutamine.

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Step 1: Preparation of the ethylene diamine amide of fusaric acid.

A solution of 7.8 g (130 mmol) of ethylene diamine in 400 mL of anhydrous THF under nitrogen was treated with 27 mmol 15 of n-butyllithium at 0° C. The solution was allowed to stir for 30 min and was treated with 5.0 g (26 mmol) of neat methyl fusarate (from step 1 of Example 690) by syringe. The reaction was kept at 0°C for 2 hr and stirred at ambient temperature overnight. The reaction was quenched with water, filtered, and 20 concentrated in vacuo. Purification by silica gel chromatography gave 3.8 g (66%) of pure amide: NMR (DMSO-d₆) δ 0.90 (t, \underline{J} = 8 Hz, 3H), 1.23-1.38 (m, 2H), 1.52-1.64 (m, 2H), 2.67 (t, J = 8 Hz, 2H), 2.74 (t, J = 8 Hz, 2H), 3.18-3.30 (br s, 2H), 3.34 (q, J = 8Hz, 2H), 7.82 d of d, \underline{J} = 9 Hz and 2 Hz, 1H), 7.96 (d, \underline{J} = 9 Hz, 25 1H), 8.47 (d, J = 2 Hz, 1H), 8.75 (t, J = 8 Hz, 1H).

Step 2: Preparation of N-[2-[[(5-butyl-2-pyridinyl)carbonyl]aminolethyl]-L-glutamine.

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Under nitrogen, a solution of 26.8 g (88.5 mmol) of N-Boc-L- γ -glutamic acid- α -t-butyl ester (BACHEM) in 125 mL of

methylene chloride was treated with 9.14 g (44.3 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction was allowed to stir for 2 hr prior to filtration under a nitrogen atmosphere. The anhydride solution was slowly added to a solution of 8.5 g (38.5 mmol) of the ethylene diamine amide from step 1 in 100 mL of methylene chloride. The reaction was allowed to stir overnight and was concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with 1M K2CO3 followed by water, dried (MgSO₄) and reconcentrated in vacuo to give the protected coupled product; a solution of this material in 250 mL of methylene chloride was cooled to 0°C and treated with 250 mL of trifluoroacetic acid (TFA). The reaction was allowed to warm to ambient temperature and stir overnight; the course of the reaction was monitored by analytical LC. Concentration in vacuo gave N-[2-[[(5-butyl-2-pyridinyl)carbonyl]amino]ethyl]-Lglutamine.

Example 861

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 N^2 -acetyl-N-[2-[[(5-butyl-2-pyridinyl)carbonyl]amino]ethyl]-L-glutamine.

The compound of Example 860 was dissolved in 150 mL of acetonitrile/water (1:1) and the pH adjusted to 9 with 2 M K_2CO_3 . The solution was cooled to 0°C and 2.27 mL (24 mmol) of acetic anhydride and 12 mL (24 mmol) of 2 M K_2CO_3 was added every 30

min. for 5 h; the pH was maintained at 9 and the reaction temperature kept below 5°C. After the last addition, the reaction was allowed to warm to ambient temperature overnight. The pH was adjusted to 3 with 3 M HCl and concentrated to 300 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) using isocractic 30% acetonitrile/water (0.05% TFA) gave 7.8 g (52% overall yield from the amide of step 1) of colorless product; an analytical sample was recrystallized from acetonitrile and then water: mp 156-158°C; Anal. Calcd for C19H28N4O5°0.83 TFA: C, 57.32; H, 7.00; N, 13,96; F, 1.14%. Found: C, 57.22; H, 7.07; N, 13.88; F, 1.07.

Example 862

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2-amino-5-[4-[(5-butyl-2-pyridinyl)carbonyl]-1-piperazinyl]-5-oxopentanoic acid.

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Step 1: Preparation of the piperizine amide of fusaric acid.

A solution of 11.20 g (130 mmol) of piperazine in 400 mL of anhydrous THF under nitrogen was treated with 27.3 mmol of n-buytyllithium at 0°C. The solution was allowed to stir for 30 min and was treated with 5.0 g (26 mmol) of neat methyl fusarate (from step 1 of Example 690) by syringe. The reaction was kept at 0°C for 2 hr and stirred at ambient temperature overnight. The reaction was quenched with water, filtered, and concentrated in vacuo. Purification by silica gel chromatography using chloroform/methanol (70:30) gave 5.82 g (90%) of pure amide: NMR (CDC13)8 0.94 (t, J = 8 Hz, 3H), 1.28-1.45 (m, 2H), 1.55-1.67 (m, 2H), 1.66-1.72 (br s, 1H), 2.64 (t, J = 8 Hz, 2H), 2.86 (t, J = 6

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Hz, 2H), 2.97 (t, $\underline{J} = 6$ Hz, 2H), 3.58 (t, $\underline{J} = 6$ Hz, 2H) 3.77 (t $\underline{J} = 6$ Hz, 2H), 7.54-7.63 (m, 2H), 8.37-8.43 (br s, 1H).

Step 2: <u>Preparation of 2-amino-5-[4-[(5-butyl-2-byridinyl)carbonyl]-1-piperazinyl]-5-oxopentanoic acid</u>

Under nitrogen, a solution of 17.4 g (57 mmol) of N-Boc-L- γ -glutamic acid- α -t-butyl ester (BACHEM) in 100 mL of anhydrous THF was treated with 5.57 g (27 mmol) of solid dicyclohexylcarbodimide (DCC). The reaction was allowed to stir 10 for 2 hr prior to filtration under a nitrogen atmosphere. The anhydride solution was slowly added to a solution of 5.82 g (23.5 mmol) of the piperazine amide from step 1 in 50 mL of anhydrous The reaction was allowed to stir overnight and was The residue was dissolved in ethyl concentrated in vacuo. 15 acetate, washed with 1M K2CO3 followed by water, dried (MgSO4), and reconcentrated in vacuo to give the protected coupled. product; a solution of this material in 150 mL of methylene chloride was cooled to 0°C and treated with 150 mL of trifluoroacetic acid (TFA) under nitrogen. The reaction was 20 allowed to warm to ambient temperature and stir overnight; the course of the reaction was monitored by analytical LC. Concentration in vacuo gave 2-amino-5-[4-[(5-butyl-2pyridinyl) carbonyl]-1-piperazinyl]-5-oxopentanoic acid.

Example 863

5 2-(acetylamino)-5-(4-[(5-butyl-2-pyridinyl)carbonyl]-1-piperazinyl]-5-oxopentanoic acid.

The compound of Example 862 was dissolved in 150 mL of acetonitrile/water (1:1) and the pH adjusted to 9 with 1 M K₂CO₃.

The solution was cooled to 0°C and 2.36 mL (25 mmol) of acetic anhydride and 25 mL (25 mmol) of 1 M K₂CO₃ was added every 30 min. for 5 h; the pH was maintained at 9 and the reaction temperature kept below 5°C. After the last addition, the reaction was allowed to warm to ambient temperature overnight.

The pH was adjusted to 4 with 3 M HCl and concentrated to 300 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) using isocratic 25% acetonitrile/water (0.05% TFA) gave 8.13 g (78%) of colorless product: MS (FAB) m/e (rel intensity)

419 (100), 258 (10), 248 (37), 205 (28); HRMS. Calcd for M+H: 20 419.2294. Found: 419.2250.

Example 864

N²-acetyl-N-[2-[[5-butyl-2-pyridinyl)carbonyl]amino]ethyl]-Lglutamine, ethyl ester.

A suspension of 57.77 g (0.133 mol) of the compound of Example 858 in CH3CN/H2O (1:1) was treated with

- 2 equivalents of 1 M K2CO3 at 0°C. With efficient stirring, 133 10 mL (0.133 mol) of 1 M K_2CO_3 and 12.5 mL (0.133 mol) of acetic anhydride were added every thirty minutes for 5 h, until a total of 10 equivalents of 1 M K2CO3 and acetic anhydride had been added. The reaction was kept at 0°C for
- 4 h then allowed to warm to room temperature overnight. The 15 reaction mixture was filtered, the filtrate cooled to 0°C, and the pH adjusted to pH 4 by the careful addition of cold dilute HCl. All volatiles were removed in vacuo. The product was dissolved in absolute ethanol and allowed to stir at reflux for 30 min. Concentration provided 45.0 g of material of which 28.0 20 g was purified by reverse phase chromatography (Waters Deltaprep-3000) using isocratic 30% acetonitrile/water (0.05% TFA); 9.0 g of pale lavender material was collected which was redissolved in 150 mL of acetonitrile and precipitated with 500 mL of water.
- This material was collected by filtration and relyophilized in 25 acetonitrile/water (1:1) to give 8.1 g (25%) of colorless ethyl ester: NMR (DMSO-d6) d 0.86(t, J = 7Hz, 3H), 1.16(t, J = 7H, 3H), 1.21-1.34 (m, 2H), 1.49-1.61 (m, 2H), 1.82 (s, 3H), 2.22 (t, J =8Hz, 2H), 2.65(t, J = 8Hz, 2H), 4.02-4.11(m, 2H), 4.15-4.24(m,
- 1H), 7.78-7.83 (m, 1H), 7.87-7.92 (m, 1H), 8.21-8.27 (m, 1H), 30

8.47(d, J = 2H, 1H), 9.94(d, J = 2H, 1H); HRMS. Calc'd for M + H: 393.2138. Found: 393.2097.

The following Examples #865-#1097 of Table XIII are highly preferred conjugates composed of dopamine- β -hydroxylase inhibitor compounds and glutamic acid derivatives. These dopamine- β -hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula XIV and XV, above.

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TABLE XIII

EXAMPLE NO.	L	R ⁹⁷	E	P
865	NHNH ,	С2Н5	CH3	H
866	NHNH	С2Н5	CH3	COCH 3
867	NHNH	С3Н7	Н	н
868	NHNH	С3Н7	Н	COCH 3
869	NHNH	С3Н7	CH3	H
870	NHNH	С3Н7	CH3	COCH 3
871	NHNH	СН3	Н	H
872	NHNH	СН3	н	COCH 3
873	NHNH	C ₄ H ₉	CH ₃	Н
874	NHNH	C4H9	CH3	COCH 3
875	NHNH	C5H11	н	н
876 ·	NHNH	C5H11	Н	COCH 3

EXAMPLE NO.	L .	R ⁹⁷	E	P	
NO.	· · · · · · · · · · · · · · · · · · ·				
877	NHNH	C5H ₁₁	СНЗ	н	
878	· NHNH	C5H11	СНЗ	COCH 3	
879	NHNH .	C6H13	Н	Н	
880	NHNH	C6H13	Н	COCH 3	
881	NHNH	C6H13	СНЗ	COCH 3	
882	NHNH	0CH 3	Н	Н	
883	NHNH	OCH 3	Н	COCH 3	
884	NHNH ·	OCH 3	СНЗ	н	
885	NHNH	0CH 3	СНЗ	COCH 3	
886	NHNH	0С ₂ Н ₅	Н	Н	
887	NHNH	ос ₂ н ₅	Н	COCH 3	
888	NHNH	∞ ₂ н ₅	СНЗ	Н	
889	NHNH	ос ₂ н ₅	СНЗ	COCH 3	
890	NHNH	0С3Н7	Н	Н	
891	NHNH	0С3Н7	Н	сосн 3	
892	NHNH	∞3н7	СНЗ	Н	

EXAMPLE NO.	L	R ⁹⁷	E	P	
893	NHNH	OC3H7	СНЗ	COCH 3	* .
894	NHNH	OC4H9	Н	Н	
895	NHNH	OC4H9	H	COCH 3	
896	NHNH	OC4H9	СН3	Н	
897	NHNH	OC4H9	СН3	COCH 3	
898	NHNH	SCH3	Н	Н	
899	NHNH	SCH3	Н	COCH 3	
900	NHNH	SCH 3	СНЗ	Н	
901	NHNH	SCH 3	CH3	COCH 3	
902	NHNH	SC2H5	н	H	
903	NHNH	SC2H5	н	COCH 3	37.
904	NHNH	SC2H5	СНЗ	Н	
905	NHNH	SC2H5	CH3	COCH 3	
906	NHNH	SC3H7	н	Н	
907	NHNH	SC3H7	н	COCH 3	
908	NHNH	SC3H7	СНЗ	н	

EXAMPLE NO.	L	R97	12	. Р
909	NHNH	SC3H7	СН3	COCH 3
910	NHNH	F	н	Н
911	NHNH	F	Н	COCH 3
912	NHNH	F	СНЗ	Н
913	NHNH	F	СНЗ	COCH 3
914	NHNH	Cl	н	Н
915	NHNH	Cl	Н	COCH 3
916	NHNH	Cl	СНЗ	Н
917	NHNH	cı	СНЗ	сосн 3
918	NHNH	Br	н	Н
919	NHNH	Br	н	COCH 3
920	NHNH	Br	СНЗ	н
921	NHNH	Br	СНЗ	COCH 3
922	NHNH	I	Н	Н
923	NHNH	I	Н	COCH 3
924	ИНИН	I	СНЗ	Н

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EXAMPLE NO.	L	R ⁹⁷	E	P
925	NHNH	I	СНЗ	COCH 3
926	NHNH	CN	н	Н
927	NHNH	CN	Н	COCH 3
928	NHNH	CN	СНЗ	н
929	NHNH	CN	СНЗ	COCH 3
930	NHNH	NO2	H	н
931	NHNH	NO2	Н	COCH 3
932	NHNH	NO2	СНЗ	н
933	NHNH	NO ₂	СНЗ	COCH 3
934	NHNH	OH	Н	Н
935	NHNH	OH	н	COCH 3
936	NHNH	OH	СНЗ	Н
937	NHNH	OH	СНЗ	COCH 3
938	NHCH 2CH2NH	СНЗ	Н	н
939	NHCH 2CH2NH	CH3	Ħ	COCH 3
940	NHCH 2CH2NH	СНЗ	CH3	Н

EXAMPLE	L	R97	E	P	
NO.					
941	NHCH 2 CH2 NH	CH3	СНЗ	COCH 3	
942	NHCH 2 CH2 NH	C2H5	Н	Н	
943	NHCH 2 CH2 NH	C2H5	Н	COCH 3	
944	NHCH 2 CH2 NH	С2Н5	CH3	Н	
945	NHCH 2 CH2 NH	С2Н5	СН3	COCH 3	
946	NHCH 2CH2NH	С3Н7	н	н	
947	NHCH 2CH2NH	С3Н7	н	COCH 3	
948	NHCH 2CH2NH	C3H7	СНЗ	Н	
949	NHCH 2 CH2 NH	С3Н7	СНЗ	COCH 3	
950	NHNH	СНЗ	CH ₃	CH ₃	
951	NHNH	CH ₃	CH ₃	COCH 3	
952	NHCH 2 CH2 NH	C4H9	СНЗ	Н	
953	NHCH 2 CH2 NH	C4H9	СН3	COCH 3	•
954	NHCH 2 CH2 NH	C5H11	н	н	
955	NHCH 2 CH2 NH	C5H11	Н	COCH 3	
956	NHCH 2CH2NH	C5H11	СН3	Н	

EXAMPLE NO.	L	R ⁹⁷	E	P
957	NHCH 2 CH2 NH	C5H ₁₁	СН3	COCH 3
958	NHCH 2 CH2 NH	C6H13	Н	н
959	NHCH 2CH2NH	C6H13	н	COCH ₃
960	NHCH 2 CH2 NH	C6H13	СНЗ	H
961	NHCH 2 CH2 NH	C6H13	СНЗ	СОСНЗ
962	NHCH 2CH2NH	OCH 3	Н	H
963	NHCH2CH2NH	OCH 3	• Н	сосн 3
964	NHCH 2 CH2 NH	OCH 3	CH3	H
965	NHCH 2CH2NH	OCH 3	CH3	сосн з
966	NHCH 2 CH2 NH	OC2H5	Н	Н
967	NHCH 2CH2NH	OC2H5	. Н	COCH 3
968	NHCH 2CH2NH	OC2H5	СНЗ	н
969	NHCH 2CH2NH	OC2H5	СНЗ	сосн 3
970 .	NHCH 2CH2NH	ОС3H7	Н	н
971	NHCH 2 CH2 NH	OC3H7	H	COCH 3
972	NHCH 2 CH2 NH	OC3H7	СНЗ	Н

EXAMPLE NO.	L	R97	E	P	
973	NHCH 2CH2NH	осзн7	СНЗ	COCH 3	لت ــــــــــــــــــــــــــــــــــــ
974	NHCH 2CH2NH	ОС4H9	Н	Н	
975	NHCH 2 CH2 NH	∞4Н9	Н	COCH 3	
976	NHCH 2 CH2 NH	OC4H9	СНЗ	н	
977	NHCH 2 CH2 NH	OC4H9	СНЗ	сосн 3	
978	NHCH 2 CH2 NH	SCH 3	Н	н	•
979	NHCH 2CH2NH	SCH 3	Н	COCH 3	
980	NHCH 2CH2NH	SCH 3	СНЗ	Н	
981	NHCH 2CH2NH	SCH 3	СНЗ	COCH 3	
982	NHCH 2CH2NH	SC ₂ H ₅	Н	н	
983	NHCH 2 CH2 NH	SC2H5	Н	СОСН 3	
984	NHCH 2 CH2 NH	SC2H5	СНЗ	Н	
985	NHCH 2 CH2 NH	SC2H5	СНЗ	сосн 3	
986	NHCH 2CH2NH	SC3H7	Н	Н	
987	NHCH 2CH2NH	SC3H7	Н	COCH 3	
988	NHCH 2 CH2 NH	SC3H7	СНЗ	Н	

EXAMPLE NO.	L .	R ⁹⁷	E	P
989	NHCH2CH2NH	SC3H7	СНЗ	COCH 3
990	NHCH 2CH2NH	F	Н	Н
991	NHCH2CH2NH	F	Н	COCH 3
992	NHCH 2 CH2 NH	F	СНЗ	Н
993	NHCH 2 CH2 NH	F	СНЗ	COCH 3
994	NHCH 2 CH2 NH	CI	н	Н
995	NHCH 2 CH2 NH	CI	Н	COCH 3
996	NHCH 2CH2NH	Cl	CH3	Н
997	NHCH 2CH2NH	cı.	СНЗ	COCH 3
998	NHCH2CH2NH	Br	Н	н
999	NHCH2CH2NH	Br	H	COCH 3
1000	NHCH 2CH2NH	Br	СНЗ	Н
1001	NHCH 2CH2NH	Br	СНЗ	COCH 3
1002	NHCH 2CH2NH	I	Н	H
1003	NHCH 2CH2NH	I.	H	COCH 3
1004	NHCH 2CH2NH	I	СН3	H

EXAMPLE NO.	L	R97	E	P	
1005	NHCH 2CH2NH	I	СНЗ	COCH 3	ل
1006	NHCH 2 CH2 NH	CN	н	Н	
1007	NHCH 2 CH2 NH	CN	н	COCH 3	
1008	NHCH 2CH2NH	CN	СНЗ	Н	
1009	NHCH 2CH2NH	CN	СН3	сосн 3	
1010	NHCH 2CH2NH	NO2	Н	н	
1011	NHCH 2CH2NH	NO ₂	H	COCH 3	
1012	NHCH 2CH2NH	NO ₂	СНЗ	Н	
1013	NHCH 2 CH2 NH	NO ₂	CH3	COCH 3	
1014	NHCH 2 CH2 NH	OH	н	Н	
1015	NHCH 2 CH2 NH	OH	н	COCH 3	
1016	NHCH 2 CH2 NH	OH	СНЗ	Н	
1017	NHCH 2 CH2 NH	OH	СНЗ	COCH 3	
1018	piperzinyl	СНЗ	Н	н	
1019	piperzinyl	СНЗ	H	сосн 3	
1020	piperzinyl	СНЗ	сн3	Н	

EXAMPLE NO.	L	R ⁹⁷	E	P
1021	piperzinyl	СН3	СНЗ	COCH 3
1022	piperzinyl	C2H5	Н	Н
1023	piperzinyl	C2H5	Н	COCH 3
1024	piperzinyl	C ₂ H ₅	СНЗ	H .
1025	piperzinyl	C2H5	СНЗ	сосн 3
1026	piperzinyl	С3Н7	Н	H
1027	piperzinyl	С3Н7	Н	сосн з
1028	piperzinyl	С3Н7	CH3	H
1029	piperzinyl	С3Н7	CH3	сосн 3
1030	NHNH	C ₂ H ₅	Н	H
1031	NHNH	C ₂ H ₅	Н	сосн 3
1032	piperzinyl	C4H9	СНЗ	н
1033	piperzinyl	C4H9	CH3	COCH 3
1034	piperzinyl	C5H11	Н	Н
1035	piperzinyl	C5H ₁₁	Н	COCH 3
1036	piperzinyl	C5H11	СНЗ	н

EXAMPLE	L	R ⁹⁷	E	P
NO.				· .
1037	piperzinyl	C5H11	СНЗ	COCH 3
1038	piperzinyl	С6Н13	Н	н
1039	piperzinyl	C6H13	Н	COCH 3
1040	piperzinyl	C6H13	СН3	Н
1041	piperzinyl	C6H13	СНЗ	COCH 3
1042	piperzinyl	OCH 3	Н	Н
1043	piperzinyl	OCH 3	Н	COCH 3
1044	piperzinyl	0CH 3	СНЗ	н
1045	piperzinyl	OCH 3	СНЗ	COCH 3
1046	piperzinyl	0С2Н5	Н	н
1047	piperzinyl	0С2Н5	Н	COCH 3
1048	piperzinyl	0С2Н5	СНЗ	Н
1049	piperzinyl	0С2Н5	СНЗ	COCH 3
1050	piperzinyl	0С3Н7	Н	Н
1051	piperzinyl	осзн7	Н	COCH 3
1052	piperzinyl	осзн7	CH3	Н

EXAMPLE NO.	L	R ⁹⁷	E	P
1053	piperzinyl	OC3H7	СНЗ	COCH 3
1054	piperzinyl	OC4H9	н	H
1055	piperzinyl	0С4Н9	н	сосн 3
1056	piperzinyl	0С4Н9	СНЗ	Н
1057	piperzinyl	OC4H9	CH3	сосн 3
1058	piperzinyl	SCH 3	Н	Н
1059	piperzinyl	SCH 3	Н	COCH 3
1060	piperzinyl	SCH 3	СНЗ	Н
1061	piperzinyl	SCH 3	СНЗ	сосн 3
1062	piperzinyl	SC2H5	Н	Н
1063	piperzinyl	SC2H5	Н	COCH 3
1064	piperzinyl	SC2H5	CH3	H
1065	piperzinyl	SC2H5	СНЗ	сосн 3
1066	piperzinyl	SC3H7	Н	H
1067	piperzinyl	SC3H7	· H	сосн 3
1068	piperzinyl	SC3H7	СНЗ	Н

EXAMPLE	L	R ⁹⁷	E	P	
NO.					
1069	piperzinyl	SC3H7	СНЗ	COCH 3	
1070	piperzinyl	F	Н	Н	
1071	piperzinyl	F	н	COCH 3	
1072	piperzinyl	F	СНЗ	н	
1073	piperzinyl	F	СНЗ	COCH 3	
1074	piperzinyl	Cl	н	н	
1075	piperzinyl	CI	Н	COCH 3	
1076	piperzinyl	CI	СНЗ	Н	
1077	piperzinyl	cı	СНЗ	COCH 3	
1078	piperzinyl	Br	н	H	
1079	piperzinyl	Br	Н	COCH 3	
1080	piperzinyl	Br	СНЗ	Н	
1081	piperzinyl	Br	СНЗ	COCH 3	
1082	piperzinyl	I	Н	н	
1083	piperzinyl	I	Н	COCH 3	
1084	piperzinyl	I	СНЗ	Н	

EXAMPLE NO.	L	R ⁹⁷	E	P
1085	piperzinyl	I	СНЗ	COCH 3
1086	piperzinyl	C N	н	н
1087	piperzinyl	CN	н	сосн 3
1088	piperzinyl	CN ·	СН3	Н
1089	piperzinyl	CN	СНЗ	COCH 3
1090	piperzinyl	NO ₂	н	н
1091	piperzinyl	NO2	н	COCH 3
1092	piperzinyl	NO ₂	СН3	н
1093	piperzinyl	NO ₂	СН3	COCH3
1094	piperzinyl	OH	Н	Н
1095	piperzinyl	OH	н	COCH 3
1096	piperzinyl	OH	СН3	Н
1097	piperzinyl	OH	СНЗ	COCH 3

The following Examples #1098-#1137 of Table XIV are highly preferred conjugates composed of dopamine- β -hydroxylase inhibitor compounds and glutamic acid derivatives. These dopamine- β -hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula XIV, above.

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TABLE XIV

EXAMPLE NO.	R94	t	E	Р
1098	СО2Н	0	Н	Н
1099	СО2Н	0	Н	COCH 3
1100	CO ₂ H	0	СНЗ	н
1101	CO ₂ H	0	СНЗ	соснз
1102	CN4H	0	Н	Н
1103	CN4H	0	Н	COCH 3
1104	CN4H	0	СН3	н
1105	CN4H	0	СНЗ	сосн 3
1106	СО2Н	1	Н	Н
1107	СО2Н	1	Н	COCH 3
1108	СО2Н	1	CH3	н
1109	СО2Н	1	CH ₃	COCH 3

EXAMPLE NO.	R ⁹⁴	t	E	P
1110	CN4 H	1	H	H .
1111	CN4H	1	Н	COCH 3
1112	CN4H	1	CH3	H
1113	CN4H	1	СНЗ	COCH 3
1114	CO ₂ H	2	Н	H
1115	СО2Н	2	H	COCH 3
1116	СО2Н	2	CH3	Ĥ
1117	CO ₂ H	2	СНЗ	COCH 3
1118	CN4H	2	Н	H
1119	CN4H	. 2	Н	COCH 3
1120	CN4H	2	СНЗ	H
1121	CN4H	. 2	СНЗ	COCH 3
1122	CO ₂ H	3	Н	н
1123	CO ₂ H	3	н	сосн 3
1124	СО2Н	3	СНЗ	Ĥ
1125	CO ₂ H	3	CH3	COCH 3

EXAMPLE NO.	R ⁹⁴	t	3 .	P
1126	CN4H	3	Н	Н
1127	CN4H	3	Н	СОСН3
1128	CN4H	3	СН3	Н
1129	CN4H	. 3	CH ₃	COCH 3
1130	со2н	4	н	Н
1131	СО2Н	4	Н	сосн3
1132	СО2Н	4	СНЗ	Н
1133	СО2Н	4	СНЗ	COCH 3
1134	CN4H	4	н	Н
1135	CN4H	4	Н	СОСН3
1136	CN4H	4	CH3	Н
1137	CN4H	4	СНЗ	COCH 3

The following Examples #1138-#1377 of Table XV are highly preferred conjugates composed of dopamine- β -hydroxylase inhibitor compounds and glutamic acid derivatives. These dopamine- β -hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula XVIII, above.

TABLE XV

$$S = \bigvee_{\substack{N \\ CH_2}} R^{113}$$

$$R^{116}$$

$$R^{116}$$

$$X = -(CH_2)_n - \bigvee_{\substack{N - C - CH_2 CH_2 \\ H}} N^{-1}$$

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R116	R117	R118	E	P
1138	0	х	Н	н	OH	н	н	Н
1139	0	x	Н	н .	OH	Н	H	COCH 3
1140	0	x	н	н	OH	Н	СНЗ	H
1141	0	x	Н	Н	OH	Н	СНЗ	COCH 3
1142	0	x	Н	Н	F	Н	H	H
1143	0	x	Н	H	F	Н	H	COCH 3
1144	0	x	н	Н	F	Н	СНЗ	H
1145	0	x	Н	H	F	Н	СНЗ	COCH 3
1146	0	x	н	Н	CF3	Н	H	H
1147	0	x	Н	Н	CF3	Н	H	COCH 3
1148	0	, X	H	H	CF3	Н	СНЗ	н
1149	0	.Χ	H	H	CF3	н	CH3	COCH 3
1150	0	x	Н	OH	OH .	H	H	H
1151	0	X	Н	OH	OH	H	Н	COCH 3

EXAMPLE NO.	n	_R 11	R114	R116	R ¹¹⁷	R ¹¹⁸	E	p
1152	0	х	Н	OH	OH	Н	СНЗ	Н
1153	0	х	Н	OH	OH	H	СНЗ	COCH 3
1154	0	х	Н	F	Н	F	Н	Н
1155	0	х	Н	F	Н	F	Н	COCH 3
1156	0	х	Н	F	н	F	СНЗ	Н
1157	0	x	Н	F	H	F	CH3	COCH 3
1158	0	x	Н	CF3	H	CF3	Н	Н
1159	0	X	H	CF3	Н	CF3	н	COCH 3
1160	0	X	Н	CF3	Н	CF3	СНЗ	Н
1161	0	х	Н	CF3	Н	CF3	СНЗ	COCH 3
1162	0	Н	x	Н	OH	Н	н	H
1163	0	Н	x	Н	OH	Н	Н	COCH 3
1164	0	Н	x	Н	OH	Н	CH3	Н
1165	0	Н	X	н	OH	Н	СНЗ	COCH 3
1166	0	Н	x	Н	F	Н	Н	Н
1167	0	Н	x	Н	F	H	Н	COCH 3
1168	0	Н	х	Н	F	Н	СНЗ	Н
1169	0	Н	x	Н	F	Н	СНЗ	COCH 3
1170	0	Н	х	Н	CF3	Н	Н	Н
1171	0	Н	X	Н	CF3	Н	Н	COCH 3
1172	0	Н	х	H	CF3	н	СНЗ	Н
1173	0	Н	x	Н	CF3	Н	СНЗ	COCH 3
1174	0	Н	x	OH	OH	H	Н	Н
1175	0	Н	x	OH	OH	Н	Н	COCH 3

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R116	R ¹¹⁷	R118	E	P
1176	0	Н	х	ОН	OH	Н	CH ₃	Н
1177	0	Н	x	OH	OH	Н	СНЗ	сосн з
1178	0	Н	\mathbf{X}	F	Н	F	Н	Н
1179	0	Н	x	F	Н	F	н	COCH 3
1180	0	Н	x	F	Н	F	СН3	Н
1181	0	н	x	F	Н	F	СНЗ	COCH 3
1182	0	Н	x	CF3	H	CF3	H	Н
1183	0	H	x	CF3	Н	CF3	Н	COCH 3
1184	0	Н	X	CF3	Н	CF3	СНЗ	H (
1185	0	H	x	CF3	Н	CF3	CH3	COCH 3
1186	1	x	Н	Н	OH	H	H	H
1187	1	X	Н	H	OH	Н	Н	COCH 3
1188	1	x	H	Н	OH	H	СН3	H
1189	1	x	Н	Н	OH	Н	СНЗ	COCH 3
1190	1	x	н	Н	F	н	Н	Н
1191	1	x	H.	Н	F	Н	н	COCH 3
1192	1 .	x	Н	Н	F	Н	CH3	H
1193	1	x	Н	н	F	Н	СНЗ	COCH 3
1194	1	х	Н	Н	CF3	Н	н .	Н
1195	1	х	Н	Н	CF3	Н	Н	COCH 3
1196	1	Х	Н	Н	CF3	Н	CH3	H
1197	1	x	Н	Н	CF3	Н	CH3	C0CH 3
1198	1	X	Н	OH	OH ,	Н	Н	Н
1199	1	x	Н	OH	OH.	Н	Н	COCH 3

EXAMPLE	n	R ¹¹	R114	_R 116	R117	R118	<u> </u>	P
NO.							<i>-</i>	P
1200	1	х	Н	OH	OH	Н	СНЗ	Н
1201	1	x	н	OH	OH	Н	СНЗ	COCH 3
1202	1	x	Н	F	Н	F	Н	Н
1203	1	x	Н	F	Н	F	Н	COCH 3
1204	1	x	Н	F	Н	F	СНЗ	Н
1205	1	x	Н	F	Н	F	СНЗ	COCH 3
1206	1	X	Н	CF3	Н	CF3	н	Н
1207	1	x	н	CF3	Н	CF3	Н	C0CH 3
1208	1	x	Н	CF3	H	CF3	СНЗ	Н
1209	1	x	Н	CF3	Н	CF3	СНЗ	COCH 3
1210	1	Н	x	Н	OH	Н	н	Н
1211	1	н	x	Н	OH	Н	Н	COCH 3
1212	1	Н	x	H	OH	Н	СНЗ	Н
1213	1	Н	x	H	OH	Н	СНЗ	COCH 3
1214	1	Н	x	Н	F	Н	Н	Н
1215	1	H	x	Н	F	Н	Н	COCH 3
1216	1	Н	x	Н	F	Н	CH3	Н
1217	1	н	x	Н	F	Н	СНЗ	C0CH 3
1218	1	Н	x	Н	CF3	Н	Н	Н
1219	1	Н	x	Н	CF3	Н	Н	COCH 3
1220	1	н	x	Н	CF3	Н	СНЗ	Н
1221	1	Н	X	Н	CF3	Н	СНЗ	COCH 3
1222	1	H	x	1H	OH	Н	Н	Н
1223	1	Н	x	1H	OH	н	Н	COCH 3
•								

•								
EXAMPLE NO.	n	R ¹¹	R114	R116	R117	_R 118	E	P
1224	1	н	x	1H	OH	Н	СНЗ	H
1225	1	Н	x	1H ·	OH	Н	СНЗ	COCH 3
1226	1	Н	х	F	H	F	Н	Н
1227	1	Н	x	F	H	F	H	COCH 3
1228	1	Н	x	F	Н	F	СНЗ	Н
1229	1	H	x	F	H	. F	СНЗ	COCH 3
1230	1	H	x	CF3	H	CF3	Н	Н
1231	1	Н	x	CF3	Н	CF3	Н	COCH 3
1232	1	Ħ	x	CF3	н	CF3	СНЗ	Н
1233	1	Н	x	CF3	Н	CF3	СНЗ	COCH 3
1234	2 .	x	Н	Н	OH	Н	Н	H
1235	2	x	Н	Н	OH	H	Н	COCH 3
1236	2	x	Н	Н	OH	Н	СНЗ	H
1237	2	x	H	Н	OH	Н	CH3	COCH 3
1238	2	x	н	Н	F	н	Н	Н
1239	2	· x	Н	Н	F :	Н	Н	COCH 3
1240	2	x	Н	H	F	H	CH3	H
1241	2	х	Н	Н	F	H	СНЗ	COCH 3
1242	2	х	Н	Н	CF3	н	Н	H
1243	2	х	Н	н	CF3	н .	н	COCH 3
1244	2	х	Н	H	CF3	Н	CH3	Н
1245	2	х	Н	Н	CF3	Н	CH3	COCH 3
1246	2	х	н	OH	OH	Н	Н	Н
1247	2	х	H .	OH	OH	Н	H	COCH 3

EXAMPLE NO.	n	R11	R114	R116	R117	R ¹¹⁸	E	P
1248	2	х	Н	0H	OH	Н	СН3	Н
1249	2	X	H	OH	OН	Н	СНЗ	COCH 3
1250	2	Х	Н	F	Н	F	н	Н
1251	2	x	Н	F	H	F	H	COCH 3
1252	2	x	Н	F	Н	F	СНЗ	Н
1253	2	X	Н	F	Н	F	СНЗ	COCH 3
1254	2	x	H	CF3	Н	CF3	Н	Н
1255	2	x	Н	CF3	Н	CF3	Н	COCH 3
1256	2	x	Н	CF3	Н	CF3	СНЗ	Н
1257	2	x	Н	CF3	н	CF3	СНЗ	COCH 3
1258	2 .	Н	x	Н	OH	Н	Н	Н
1259	2	H	x	Н	OH	Н	Н	COCH 3
1260	2	Н	x	Н	OH	Н	СНЗ	Н
1261	2	. Н	X	Н	OH .	Н	СНЗ	COCH 3
1262	2	Н	x	Н	F	H	Н	Н
1263	2	Н	·x	Н	F	Н	Н	COCH 3
1264	2	H	x	Н	F	Н	СНЗ	Н
1265	2	H	x	Н	F	Н	СНЗ	COCH 3
1266	2	H	x	Н	CF3	Н	Н	н
1267	2 ′	Н	x	H.	CF3	Н	Н	COCH 3
1268	2	Н	x	Н	CF3	н	СНЗ	Н
1269	2	Н	X	Н	CF3	Н	CH3	COCH 3
1270	2	Н	X.	OH	OH	Н	H	Н .
1271	2	Н	x	OH .	OH	Н	н	COCH 3

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R116	R117	R118	E .	P		
1272	2	Н	x	OH .	OH	н	СНЗ	н		
1273	2	Н	x	OH	OH	Н	СНЗ	COCH 3		
1274	2	Н	х	F	H	F	Н	H		
1275	2	H	x	F	H	F	Н	COCH 3		
1276	2	H	x	F	Н	F	СНЗ	H		
1277	2	Н	x	F	H	F	CH3	COCH 3		
1278	2	H _.	x	CF3	H	CF3	Н	H		
1279	2	Н	x	CF3	Н	CF3	H	COCH 3		
1280	2	H	х	CF3	Н	CF3	СНЗ	H		
1281	2	Н	x	CF3	H	CF3	СНЗ	COCH 3		
1282	3	x	Н	Н	OH	H	H	H		
1283	3	x	H	Н	OH	Н	Н	COCH 3		
1284	3	x	Н	H	OH	·H	CH3	Н		
1285	3	х	H	Н	OH .	Н	СНЗ	COCH 3		
1286	3	x	H	Н	F	Н	н	H		
1287	3	х	Н	Н	F	Н	H .	COCH 3		
1288	3	x	Н	Н	F	Н	СНЗ	H		
1289	3	x	Н	Н	F	Н	СНЗ	COCH 3		
1290	3	x	H	Н	CF3	Н	Н	н		
1291	3	х	Н	Н	CF3	Н	Н	COCH 3		
1292	3	х	Н	H·	CF3	Н	СНЗ	н		
1293	3	x	Н	· H	CF3	H	СНЗ	COCH 3		
1294	3	х	Н	OH	OH	Н	H	Н		
1295	3	x	Н	OH	OH	Н	н	COCH 3		

EXAMPLE	n	R ¹¹	R ¹¹⁴	R116	R ¹¹⁷	R118	E	P
NO.							- .	
1296	3	x	Н	OH	OH	Н	СНЗ	Н
1297	3	x	Н	OH	OH	Н	СНЗ	сосн 3
1298	3	x	Н	F	Н	F	Н	Н
1299	3	x	Н	F	Н	F	H	COCH 3
1300	3	X	H	F	H	F	СНЗ	Н
1301	3	X	Н	F	Н	F	СНЗ	COCH 3
1302	3	x	Н	CF3	Н	CF3	Н	Н
1303	3	x	Н	CF3	Н	CF3	Н	COCH 3
1304	3	X	Н	CF3	Н	CF3	СНЗ	Н
1305	3	х	Н	CF3	Н	CF3	СНЗ	сосн з
1306	3	Н	x	Н	OH	H	Н	Н
1307	3	Н	X	Н	OH	Н	Н	COCH 3
1308	3	Н	X .	Н	OH	Н	CH3	Н
1309	3	H	X	Н	OH	Н	СНЗ	COCH 3
1310	3	H	X	Н	F	Н	H	Н
1311	3	Н	X	Н	F	Н	H	COCH 3
1312	3	H	x	Н	F	Н	СНЗ	Н
1313	3	Н	X	Н	F	Н	СНЗ	COCH 3
1314	3	Н	x	Н	CF3	H	Н	Н
1315	3	Н	X	н	CF3	Н	н	COCH 3
1316	3	H	X	H	CF3	Н	СНЗ	Н
1317	3	Н	x	Н	CF3	Н	СНЗ	COCH 3
1318	3	H	x	OH	OH	Н	Н	Н
1319	3	Н	x	OH	OH	Н	Н	COCH 3

		.511	p114	R ¹¹⁶	p117	p118	Te	P	 -
EXAMPLE NO.	n		K	K	X	K	.		i
1320	3	Н	x	OH	OH	н	CH3	н	
1321	3	Н	x	ОН	OH	Н	СНЗ	COCH 3	
1322	3	Н	x	F	Н	F.	Н	Н	
1323	3	Н	x	F	H	F	H .	COCH 3	
1324	3	Н	x	F	H ·	F	СНЗ	H	
1325	3	H	X	F	H	F	СНЗ	COCH 3	
1326	3	Н	x	CF3	Н	CF3	Н	н	
1327	3	Н	x	CF3	H	CF3	H.	COCH 3	
1328	3	Н	x	CF3	H	CF3	СНЗ	н	
1329	3	Н	x	CF3	Н	CF3	СНЗ	COCH 3	
1330	4	x	H	Н	OH	Н	H	Н	
1331	4	x	H	Н	OH	Н	Н	COCH 3	
1332	4	x	H	H	OH	H	CH3	H	
1333	4	x	H.	Н	OH	Н	СНЗ	сосн з	
1334	4	x	Н	H	F	Н	Н	H	
1335	4	x	Н	Н	F ·	H	Н	COCH 3	
1336	4	x	Н	Н	F	Н	СНЗ	H	
1337	4	x ·	Н	Н	F	·H	СНЗ	COCH 3	
1338	4	x	Н	Н	CF3	Н	Н	H	
1339	4	х	н .	Н	CF3	Н	н	COCH 3	
1340	4	х	Н	Н	CF3	Н	СНЗ	H	
1341	4	х	Н	Н	CF3	H	СНЗ	COCH 3	
1342	4	X	Н	OH	OH .	Н	Н	H	
1343	4	х .	Н	OH	OH .	H	Н	соснз	

EXAMPLE NO.	n	R ¹¹	R114	R116	R117	R118	E	P
1344	4	х	Н	OH	OH	Н	СНЗ	Н
1345	4	x	Н	OH	OH	Н	СНЗ	COCH 3
1346	4	X	Н	F	H	F	Н	Н
1347	4	x	H	F	Н	F	Н	COCH 3
1348	4	x	Н	F	Н	F	СНЗ	Н
1349	4	x	Н	F	Н	F	снз	COCH 3
1350	4	x	Н	CF3	H	CF3	н	н
1351	4	· ×	Н	CF3	H	CF3	Н	COCH 3
1352	4	x	Н	CF3	Н	CF3	СНЗ	Н
1353	4	x	H	CF3	Н	CF3	СНЗ	COCH 3
1354	4	H	x	H	OH	Н	Н	Н
1355	4	H	x	Н	OН	H	н	COCH 3
1356	4	Н	x	н	OH	Н	СНЗ	н
1357	4	Н	x	Н	OH	H	СНЗ	COCH 3
1358	4	H	x	н .	F	Н	Н	Н
1359	4	H ·	x	H	F	Н	Н	COCH 3
1360	4	H	· x	Н	F	Н	СНЗ	H
1361	4	H	x	H	F	Н	СНЗ	COCH 3
1362	4	H	X	Н	CF3	Н	Н	Н
1363	4	Н	x	H	CF3	Н	Н	COCH 3
1364	4	H	x	Н	CF3	H	СНЗ	Н
1365	4	H	x	Н	CF3	Н	CH3	COCH 3
1366	4	H	x	OH	OH	Н	Н	Н
1367	4	Н	x	OH	OH	Н	Н	СОСН 3

EXAMPLE NO.	n	R ¹¹	R114	_R 116	R117	R118	E	P
1368	4	н	х	OН	OH	H .	СНЗ	Н
1369	4	Н	x	OH	OH	Н	CH3	COCH 3
1370	4	Н	x	F	H .	F	H	Н
1371	4	Н	x	F	Н	F	H	COCH 3
1372	4	Н	x	F	H .	F	CH3	H
1373	4	н	x	F	H	F	СНЗ	сосн 3
1374	4	Н	x	CF3	Н	CF3	H	H
1375	4	Н	x	CF3	н	CF3	н	COCH 3
1376	4	Н	x	CF3	Н	CF3	CH3	H
1377	4	Н	x	CF3	Н	CF3	CH3	COCH 3

The following Examples #1378-#1497 of Table XVI are highly preferred conjugates composed of dopamine- β -hydroxylase inhibitor compounds and glutamic acid derivatives. These dopamine- β -hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula XVIII, above.

TABLE XVI

EXAMPLE NO.	n	_R 116	R117	R118	E	P
1378	0	н	OH	Н	Н	Н
1379	0	Н	OH	Н	Н	СОСН 3
1380	0	Н	OH	Н	СНЗ	н
1381	0	H ·	OH	Н	СНЗ	COCH 3
1382	0	Н	F	Н	Н	Н
1383	0	Н	F	Н	Н	COCH 3
1384	0	Н	. F	Н	СНЗ	н
1385	0	H _.	F	Н	СНЗ	COCH 3
1386	0	Н	CF ₃	Н	Н	Н
1387	0	Н	CF3	Н	Н	COCH 3
1388	0	Н	CF3	H	СНЗ	Н

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						<u> </u>
EXAMPLE NO.	n	_R 116	R117	R118	E	P
1389	0	. Н	CF3	Н	CH3	COCH 3
1390	0	OH	ОН	н	Н	H
1391	0	OH	OH	Н	H	COCH 3
1392	Ö	OH	OH	Н .	СН3	Н
1393	0	OH	OH	Н	CH3	COCH 3
1394	0	F	H	F	Н	H
1395	0	F	Н	F	H	сосн 3
1396	0	F	н	F	СНЗ	H
1397	0	F	н	F.	СНЗ	COCH 3
1398	0	CF3	Н	CF3	Н	H
1399	0	CF3	н	CF3	Н	COCH 3
1400	0	CF3	Н	CF3	CH3	н
1401	0	CF3	Н	CF3	CH3	COCH 3
1402	1 .	Н	OH	н	Н	н
1403	1	Н	OH	Н	Н	COCH 3
1404	1	Н	OH	Н	СНЗ	Н

EXAMPLE NO.	n	R116	R117	R118	E	P
1405	1	Н	OH	Н	СНЗ	COCH 3
1406	1	Н	F	Н	н	Н
1407	1	Н	F	Н	Н	COCH 3
1408	1	Н	F	Н	СНЗ	Н
1409	1	Н	F	Н	СНЗ	сосн з
1410	1	. н	CF3	H'	Н	н
1411	1	Н	CF3	Н	н	COCH 3
1412	1	Н	CF3	н	СН3	Н
1413	1	Н	CF3	Н	СН3	COCH 3
1414	1	OH	OH	Н	Н	Н
1415	1	OH	OH	н	н	COCH 3
1416	1	OH	OH	н	СНЗ	Н
1417	1	ОН	ОН	Н	СНЗ	COCH 3
1418	1	F	Н	F	Н	н
1419	1	F	Н	F	Н	COCH 3
1420	1	F	Н	F	СНЗ	Н

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EXAMPLE NO.	n	R116	R ¹¹⁷	R118	E·	P
1421	1	F	н	F	СНЗ	COCH 3
1422	1	CF3	Н .	CF3	н	Н
1423	1	CF3	Н	CF3	Н	COCH 3
1424	1	CF3	Н	CF3	CH3	Н
1425	1	CF3	Н	CF3	СНЗ	COCH 3
1426	2	Н	OH	Н	Н	H
1427	2	H	OН	Н	Н	COCH 3
1428	2	Н	OH	н	СНЗ	Н
1429	2	Н	ОH	н	СНЗ	COCH 3
1430	2	Н	F	Н	Н	H
1431	2	н	F	H.	Н	COCH 3
1432	2	Н	F	H	СНЗ	Н
1433	2	н	F	н	СНЗ	COCH 3
1434	2	Н	CF3	н∙	Н	H
1435	2 .	Н	CF3	H	Н	COCH 3
1436	2	Н	CF3	Н	CH3	• н

EXAMPLE NO.	n	R116	R117	R118	E	P
1437	2	Н	CF3	Н	CH3	COCH 3
1438	2	OH	OH	Н	Н	\mathbf{H}°
1439	2	OH	OH	Н	Н	COCH 3
1440	2	OH	OH	н	СНЗ	Н
1441	2	OH	OH	Н	СН3	COCH 3
1442	2	F	Н	F	н	Н
1443	. 2	F	Н	F	н	COCH 3
1444	2	F	Н	F	CH ₃	H
1445	2	F	н	F	сн3	COCH 3
1446	2	CF3	н	CF3	Н	Н
1447	2	CF3	н	CF3	Н	COCH 3
1448	2	CF3	Н	CF3	CH3	H
1449	2	CF3	Н	CF3	СНЗ	COCH 3
1450	3	Н	OH	н	н	Н
1451	3	H	OH	Н	н	COCH 3
1452	3	Н	OH	Н	СНЗ	Н

EXAMPLE NO.	n	R116	R117	R118	E ·	P
	<u> </u>					
1453	3	н	OH	Н	CH3	COCH 3
1454	3	н	F	н	Н	н
1455	3	Н	F	н	H .	COCH 3
1456	3	Н	F	н	СНЗ	н
1457	3	Н	F	Н	CH3	COCH 3
1458	3	Н	CF3	Н	Н	H
1459	3	Н	CF3	н	Н	COCH 3
1460	3	Н	CF3	Н	СНЗ	Ĥ
1461	3	Н	CF3	н	CH3	COCH 3
1462	3	OН	OH	Н	Н	н
1463	3	ОH	OH	Н	н	COCH 3
1464	3	OH	OH	н	СНЗ	н
1465	3	OН	OH	Н	CH3	COCH 3
1466	3	F	Н	F	H	H
1467	3	F	H	F	Н	сосн 3
1468	3	F	н	F	СНЗ	H 1

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EXAMPLE NO.	n	R ¹¹⁶	R ¹¹⁷	R118	E	P
1469	3	F	Н	F	СНЗ	COCH 3
1470	3	CF3	Н	CF3	Н	Н
1471	3	CF3	H	CF3	н	COCH 3
1472	3	CF3	Н	CF3	СНЗ	Н
1473	3	CF3	Н	CF3	СНЗ	COCH 3
1474	4	Н	OH	Н	Н	Н
1475	4	Н	OН	Н	н	COCH 3
1476	4	Н	OН	н	СНЗ	Н
1477	4	Н	OH	Н	CH3	COCH 3
1478	4	Н	F	Н	н	н
1479	4	Н	F	Н	н	COCH 3
1480	4	Н	F	Н	СНЗ	Н
1481	4	Н	F	Н	СНЗ	COCH 3
1482	4	Н	CF3	Н	Н	Н
1483	4	Н	CF3	Н	Н	COCH 3
1484	4	Н	CF3	Н	СНЗ	Н

EXAMPLE NO.	n ·	_R 116	R117	R118	E	P
L	· ·					
1485	4	Н	CF3	Н	CH3	COCH 3
1486	4	OH	OH	H	н	Н
1487	4	OH	OH	H _.	н .	COCH 3
1488	4	OH	OH	\mathbf{H}_{\perp}	СН3	Н
1489	4	OH	ОН	Н	CH3	COCH 3
1490	4	F	Н	F	Н	Н
1491	4	F	Н	F	Н	COCH 3
1492	4	F	Н	F	СН3	Н
1493	4	F	Н	F	CH3	COCH 3
1494	4	CF3	Н	CF3	Н	Н
1495	4	CF3	н	CF3	Н	COCH 3
1496	4	CF3	н	CF3	CH3	Н
1497	4	CF3	Н	CF3	CH3	COCH 3

The following Examples #1498-#1857 of Table XVII are highly preferred conjugates composed of dopamine- β -hydroxylase inhibitor compounds and glutamic acid derivatives. These dopamine- β -hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula XVIII, above.

TABLE XVII

EXAMPLE NO.	n	L	R116	R ¹¹⁷	R118	E	P
1498	0	NHNH	Н	OH	Н	н	Н
1499	0	NHNH	Н	OH	Н	Н	COCH 3.
1500	0	NHNH	Н	OH	Н	СН3	Н
1501	0	NHNH	Н	OH	Н	СНЗ	COCH 3
1502	0	NHNH	Н	F	H	Н	Н
1503	0	NHNH	Н	F	H	н	сосн 3
1504	0	NHNH	Н	F	Н	СНЗ	Н
1505	0	NHNH	H.	F	Н	СН3	COCH 3
1506	0	NHNH	н	CF3	н	Н	Н
1507	0	NHNH	Н	CF3	Н	Н	COCH 3
1508	0	NHNH	н	CF3	н	CH ₃	Н

EXAMPLE NO.	n	L	R116	R117	R118	E	P
1509	0	NHNH	Н	CF3	Н	СН3	COCH 3
1510	0	NHNH	OH	OH	Н	Н.	н
1511	0	NHNH	OH	OH	н	Н	сосн 3
1512		NHNH	OH	OH	Н	СН3	H
1513	0	NHNH	OH	OH	н	СНЗ	COCH 3
1514	0	NHNH	F	H	F	H	* H
1515	0	NHNH	_. F	H	F .	н	COCH3
1516	0	NHNH	F	H	F	СН3	Н
1517	0	NHNH	F	Н	F	СН3	COCH 3
1518	0	NHNH	CF ₃	Н	CF ₃	Н	H
1519	0	NHNH	CF3	H	CF ₃	Н	COCH 3
1520	0	NHNH	CF ₃	Н	CF3	СНЗ	. H →
1521	0	NHNH	CF3	H	CF ₃	CH ₃	COCH 3
1522	0	NHCH 2CH2NH	H ·	OH .	Н	Н	H
1523	0	NHCH 2CH2NH	Н	OH	Н	н	сосн з
1524 .	0.	NHCH 2CH2NH	н	OH	н	Снз	H

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EXAMPLE	· ·	n L R116 R117 P11					
NO.			Razo	R117	R118	E	P
1525	0	NHCH 2CH2NH	н	OH	Н	CH ₃	COCH 3
1526	0	NHCH 2CH2NH	Н	F	Н	н	Н
1527	0	NHCH 2CH2NH	н	F	Н	Н	сосн 3
1528	0	NHCH 2CH2NH	Н	F	Н	СН3	Н
1529	0	NHCH 2CH2NH	Н	F	Н	СН3	сосн 3
1530	0	NHCH 2CH2NH	н	CF3	Н	н	Н
1531	0	NHCH 2CH2NH	Н	CF3	н	н	COCH 3
1532	0	NHCH 2CH2NH	н	CF3	Н	CH ₃	н
1533	0	NHCH 2CH2NH	Н	CF3	Н	СНЗ	COCH 3
1534	0	NHCH 2CH2NH	OH	OH	Н	Н	Н
1535	0	NHCH 2CH2NH	OH	OH	Н	Н	COCH 3
1536	0	NHCH 2CH2NH	OH	OH	н	СН3	н
1537	0	NHCH 2CH2NH	OH	OH	н	СН3	COCH 3
1538	0	NHCH 2CH2NH	F	н	F	Н	н
1539	0	NHCH 2CH2NH	F	Н	F	Н	СОСН 3
1540	0	NHCH 2CH2NH	F	Н	F	CH ₃	н
1541	0	NHCH 2CH2NH	F	Н	F	СН3	COCH 3

EXAMPLE NO.	n	L	_R 116	R117	R118	E	P
1542	0	NHCH 2CH2NH	CF3	Н .	CF ₃	·H	Н
1543	0	NHCH 2CH2NH	CF3	^н н	CF ₃	Н	COCH 3
1544	0	NHCH 2CH2NH	CF ₃	Н	CF3	СНЗ	H
1545	0	NHCH 2CH2NH	CF3	н	CF3	СН3	сосн 3
1546	0	piperazinyl	Н	OH	Н	H	Н
1547	0	piperazinyl	н	OH	Н	Н	COCH 3
1548	0.	piperazinyl	Н	OH	Н	СН3	H
1549	0	piperazinyl	Н	OH	Н	CH ₃	COCH 3
1550	0	piperazinyl	Н	F	Н	Н	H
1551	0	piperazinyl	Н	F	H	Н	COCH 3
1552	0	piperazinyl	н	F	Н	CH3	H
1553	0	piperazinyl	н	F	Н	CH3	COCH 3
1554	0	piperazinyl	Н	CF3	H	Н	Н
1555	0	piperazinyl	Н	CF ₃	Н	Н	COCH 3
1556	0	piperazinyl	Н	CF ₃	H .	CH3	H
1557	0	piperazinyl	Н	CF3	Н	СНЗ	COCH 3

EXAMPLI NO.	E 1	ı L	_R 116	R ¹¹⁷	R ¹¹⁸	E	P
	-						
1558	C	piperazinyl	OH	OH	Н	Н	Н
1559	0	piperazinyl	OН	OH	Н	Н	COCH 3
1560	0	piperazinyl	OH	OH	н	СНЗ	н
1561	0	piperazinyl	OH	OH	Н	СНЗ	COCH 3
1562	0	piperazinyl	F	Н	F	н	Н
1563	0	piperazinyl	F	H	F	H.	COCH 3
1564	0	piperazinyl	. F	H	F	СН3	н
1565	0	piperazinyl	F	Н	F	СНЗ	COCH 3
1566	0	piperazinyl	CF ₃	Н	CF3	Н	Н
1567	0	piperazinyl	CF3	Н	CF ₃	н	COCH 3
1568	0	piperazinyl	CF ₃	н	CF3	СН3	Н
1569	0	piperazinyl	CF3	H	CF3	СНЗ	COCH 3
1570	1	NHNH	Н	OH	н	н	H
1571	1	NHNH	H	OH	н	Н	COCH 3
1572	1	NHNH	Н	OH	Н	СНЗ	Н
1573	1	NHNH	Н	OH	н	СНЗ	COCH 3

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						•	
EXAMPLE NO.	n	L	_R 116	_R 117	R118	E	P
1574	1	NHNH	Н	F	Н	Н	Н
1575	1	NHNH	Н	F	Н	Н	COCH 3
1576	1	NHNH	Н	F	н	СНЗ	H
1577	1	NHNH	'H	F	Н	СНЗ	COCH 3
1578	1	NHNH	Н	CF3	Н	н	Н
1579	1	NHNH	Н	CF3	H	Н	сосн 3
1580	1	NHNH	Н	CF3	Н	СНЗ	Н
1581	1	NHNH	H	CF3	Н	СНЗ	COCH 3
1582	1	NHNH	OH	OH	Н	н	Н
1583	1	ИНИН	OH	OH	Н	Н	COCH 3
1584	1	NHNH	OH	OH	H	СНЗ	н
1585	1	NHNH	OH	OH	Н	СНЗ	COCH 3
1586	1	NHNH	F	H	F	H	н
1587	1	NHNH	F	Н	F	н	COCH 3
1588	1	NHNH	F	H ·	F	СНЗ	H
1589	1	NHNH	F	н	F	СНЗ	COCH 3
1590	1	NHNH	CF3	H	CF3	Ĥ	H

EXAMPLE	I	L L	R116	R117	_R 118	E	p
NO.							<i>E</i>
1591	1	NHNH	·CF3	Н	CF ₃	Н	сосн 3
1592	1	NHNH	CF3	н	CF3	СН3	Н
1593	1	NHNH	CF ₃	н	CF3	СНЗ	сосн 3
1594	1	NHCH 2CH2NH	н	OH	н	н	н
1595	1	NHCH 2CH2NH	Н	OH	·H	Н	сосн 3
1596	1	NHCH 2CH2NH	Н	OH	Н	СНЗ	Н
1597	1	NHCH 2CH2NH	Н	OH	Н	СН3	COCH 3
1598	1	NHCH 2CH2NH	Н	F	Н	н	Н
1599	1	NHCH 2CH2NH	Н	F	н	Н	COCH 3
1600	1	NHCH 2CH2NH	Н	F	Н	СНЗ	Н
1601	1	NHCH 2CH2NH	H	F	Н .	CH3	COCH 3
1602	1	NHCH 2CH2NH	H	CF3	Н	Н	Н
1603	1	NHCH 2CH2NH	Н	CF3	H	Н	COCH 3
1604	1	NHCH 2CH2NH	Н	CF3	Н	CH3	Н
1605	1	NHCH 2CH2NH	Н	CF3	Н	СНЗ	COCH 3
1606	1	NHCH 2CH2NH	OH	OH	Н	Н	Н

EXAMPLE NO.	n	L.	R116	R117	R118	E	P
1607	1	NHCH 2CH2NH	OH	OH	Н	Н	COCH3
1608	1 .	NHCH 2CH2NH	OH .	OH	Н	CH ₃	H .
1609	1	NHCH 2CH2NH	OH	OH	H	СН3	COCH 3
1610	1	NHCH 2CH2NH	F	H	F	H	H]
1611	1	NHCH 2CH2NH	F	H	F	Н	COCH 3
1612	1	NHCH 2CH2NH	F	Н	F	СНЗ	H
1613	1	NHCH 2CH2NH	F	H	F	СНЗ	COCH 3
1614	1	NHCH 2CH2NH	CF3	Н	CF3	Н	H
1615	1	NHCH 2CH2NH	CF3	H :	CF3	Н	сосн 3
1616	1	NHCH 2CH2NH	CF3	Н	CF3	CH ₃	Ħ
1617	1	NHCH 2CH2NH	CF3	H	CF3	СНЗ	сосн 3
1618	1	piperazinyl	H ·	OH	Н	H	H
1619	1	piperazinyl	Н	OH	н	H .	COCH 3
1620	1	piperazinyl	н	OH	н	СНЗ	н
1621	1	piperazinyl	н	OH	н	СНЗ	COCH 3
1622	1	piperazinyl	Н	F	н	Н	Н
1623	1	piperazinyl	Н	F	H	Н	COCH 3

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EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R118	E	р
						7 <u> 1 </u>	
1624	1	piperazinyl	Н	F	Н	СНЗ	Н
1625	1	piperazinyl	Н	F	Н	CH ₃	COCH 3
1626	1	piperazinyl	Н	CF3	Н	Н	Н
1627	1	piperazinyl	Н	CF3	Н	н	COCH 3
1628	1	piperazinyl	Н	CF3	Н	СН3	Н
1629	1	piperazinyl	Н	CF3	Н	СНЗ	COCH 3
1630	1	piperazinyl	OH	OH	H	н	Н
1631	1	piperazinyl	OH	OH	Н	н	COCH 3
1632	1	piperazinyl	OH	OH	Н	СН3	н
1633	1	piperazinyl	OH	ОН	Н	СН3	COCH 3
1634	1	piperazinyl	F	Н	F	Н	Н
1635	1	piperazinyl	F	H	F	Н	COCH 3
1636	1	piperazinyl	F .	н .	F	CH ₃	н
1637	1	piperazinyl	F	Н	F	СНЗ	COCH 3
1638	1	piperazinyl	CF3	Н	CF3	н	Н
1639	1	piperazinyl	CF3	Н	CF3	Н	COCH 3

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EXAMPLE NO.	n	L	R116	R117	R118	E	P
1640	1	piperazinyl	CF3	Н	CF3	СН3	Н
1641	1	piperazinyl	CF3	н	CF ₃	СН3	сосн з
1642	2	NHNH	H .	OH .	н	Н	H
1643	2	. NHNH	Н	OH	н	Н	сосн 3
1644	2	NHNH	H	OH	н	СН3	H
1645	2	NHNH	Н	OH	Н	СН3	COCH 3
1646	2	NHNH	н	F ·	н	н	H
1647	2	NHNH	Н	F	Н	н	сосн з
1648	2	NHNH	Н	F ·	Н	СНЗ	H
1649	2	NHNH	н	F	Н	СН3	COCH 3
1650	2	NHNH	Н	CF3	Н	Н	H
1651	2	NHNH	н .	CF3	H	Н	COCH 3
1652	2	NHNH	Н	CF ₃	Н	СН3	Н
1653	2	NHNH	Н	CF3	Н	СН3.	сосн 3
1654	2	NHNH	OH	OH	Н	H	H
1655	2	NHNH	OH	ОН	н	Н .	COCH 3
1656	2	NHNH	OH :	OH	H .	СН3	Н

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EXAMPLE NO.	r	L	R116	R117	R118	E	P
					·		
1657	2	NHNH	OH	OH	Н	СН3	COCH 3
1658	2	NHNH	F	Н	F	Н	Н
1659	2	NHNH	F.	Н	F	Н	COCH 3
1660	2	NHNH	F	Н	F	СНЗ	Н
1661	2	NHNH	F	Н	F	CH ₃	СОСН 3
1662	2	NHNH	CF3	Н	CF3	н	н
1663	2	NHNH	CF3	Н	CF3	Н	сосн 3
1664	2	NHNH	CF3	Н	CF3	CH ₃	Н
1665	2	NHNH	CF ₃	Н	CF ₃	CH3	COCH 3
1666	2	NHCH 2CH2NH	Н	OH	H	н	Н
1667	2	NHCH 2CH2NH	н	OH	Н	н	COCH 3
1668	2	NHCH 2CH2NH	Н	OH	Н	СН3	н
1669	2	NHCH 2CH2NH	Н	OH	Н	СН3	сосн 3
1670	2	NHCH 2CH2NH	Н	F	н	Н	н
1671	2	NHCH 2CH2NH	Н	F	Н	Н	COCH 3
1672	2	NHCH 2CH2NH	н	F	Н	CH ₃	Н

EXAMPLE NO.	n	L	R116	R117	R118	E P	
		<u></u>	<u></u>				<u></u> 1) :-
1673	2	NHCH 2CH2NH	Н	F .	Н	Снз соснз	
1674	2	NHCH2CH2NH	Н	CF ₃	Н	H (H 2)	•
1675	2	NHCH 2CH2NH	Н	CF3	Н	н сосн3	· .
1676	2	NHCH 2CH2NH	Н	CF ₃	Н	СН3 Н	•
1.677	2	NHCH 2CH2NH	Н	CF3	Н	CH ₃ COCH ₃	
1678	2	NHCH 2CH2NH	OH	OH:	Н	н н	
1679	2	NHCH 2CH2NH	OH	OH	Н	н сосн з	
1680	2	NHCH 2CH2NH	OH	OH	Н	СН3 Н	·. :
1681	2	NHCH 2CH2NH	OH	OH	н	снз соснз	
1682	2	NHCH 2CH2NH	F	Н	F	н н	
1683	2	NHCH 2CH2NH	F	Н	F .	н сосн з	· .
1684	2	NHCH 2CH2NH	F	Н	F	СН3 Н	
1685	2	NHCH 2CH2NH	F	Н	F	СН3 СОСН3	
1686	2	NHCH 2CH2NH	CF3	H .	CF3	н н	
1687	2	NHCH 2CH2NH	CF3	H	CF3	н соснз	
1688	2	NHCH 2CH2NH	CF3	H	CF3	СН3 Н	•

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EXAMPLE	r	L	R ¹¹⁶	R117	_R 118	E	7
NO.	-			**		£	P
1689	2	NHCH 2CH2NH	CF3	Н	CF3	CH ₃	COCH 3
1690	2	piperazinyl	H	OH	н	Н	Н
1691	2	piperazinyl	Н	OH ·	Н	н	сосн 3
1692	2	piperazinyl	Н	OН	Н	СН3	н
1693	2	piperazinyl	Н	OH	Н	СН3	COCH 3
1694	2	piperazinyl	H	F	Н	Н	Н
1695		piperazinyl	н	F	Н	Н	COCH 3
1696	2	piperazinyl	Н	F	н	СНЗ	н
1697	2	piperazinyl	Н	F	н	CH ₃	COCH 3
1698	2	piperazinyl	Н	CF3	Н	Н	Н
1699	2	piperazinyl	H	CF3	н	Н	COCH 3
1700	2	piperazinyl	H	CF3	н	СН3	н
1701	2	piperazinyl	Н	CF ₃	Н	СН3	сосн 3
1702	2	piperazinyl	OН	OH	Н	Н	н
1703	2	piperazinyl	OH	OH	Н	Н	COCH 3
1704	2	piperazinyl	OH	OH	Н	СН3	Н
1705	2	piperazinyl	OH	OH	H	СН3	COCH 3

282

EXAMPLE NO.	n	L	R116	R117	R ¹¹⁸	E P
1706	2	piperazinyl	F	н	F	н н
1707	2	piperazinyl	F	Н	F	н соснз
1708	2	piperazinyl	F	H,	F	сн3 н
1709	2	piperazinyl	F.	H	F	сн ₃ сосн ₃
1710	2	piperazinyl	CF3	Н	CF3	н н
1711	2	piperazinyl	CF3	Н	CF3	н соснз
1712	2	piperazinyl	CF3	Н	CF3	СН3 Н
1713	2	piperazinyl	CF3	н	CF3	CH ₃ COCH ₃
1714	3	NHNH	Н	OH	Н	н н
1715	3	NHNH	Н	OH	н	н соснз
1716	3	NHNH	Н	OH	н	СН3 Н
1717	3	NHNH	H	OH	Н	CH ₃ COCH ₃
1718	3	NHNH	H	F	н	н н
1719	3	NHNH	H	F .	Н	н соснз
1720	3	NHNH	Н	F	Н	СН3 Н
1721	3	NHNH	H	F	Н	Снз СОСНЗ

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EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R118	Е	P
1722	3	MBRI	11				
1122	3	NHNH	Н	CF3	H	Н	Н
1723	3	ИНИН	H	CF3	Н	Н	COCH 3
1724	3	NHNH	Н	CF3	Н	СН3	Н
1725	3	NHNH	Н	CF3	Н	СН3	COCH ₃
1726	3	NHNH	OH	OH	Н	Н	Н
1727	3	NHNH	OH	OH .	Н	Н	сосн 3
1728	3	NHNH	OH	OH	н	СН3	Н
1729	3	NHNH	OH	OH	Ħ	CH ₃	COCH 3
1730	3	NHNH	F	н	F	Н	Н
1731	3	NHNH	F	H	F	Н	COCH 3
1732	3	NHNH	F	Н	F	СНЗ	н
1733	3	NHNH	F	Н	F	СНЗ	COCH 3
1734	3	NHNH ·	CF3	Н	CF3	Н	Н .
1735	3	NHNH	CF3	Н	CF3	Н	COCH 3
1736	3	NHNH	CF3	Н	CF3	СН3	н
1737	3	NHNH .	CF3	Н	CF3	СН3	сосн 3
1738	3	NHCH 2CH2NH	Н	OH	Н	Н	Н

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R118	E	P
1739	3	NHCH 2CH2NH	Н	OH	Н	H	COCH 3
1740	3	NHCH 2CH2NH	Н	OH	Н	СН3	H
1741	3	NHCH 2CH2NH	н	OH	Н	СН3.	COCH3
1742	3	NHCH 2CH2NH	н	F	Н	н	H
1743	3	NHCH 2CH2NH	Н	F .	Н	Н	COCH 3
1744	3	NHCH 2CH2NH	Н	F	Н	СН3	Н
1745	3	NHCH 2CH2NH	н	F	Н	СНЗ	COCH 3
1746	3	NHCH 2CH2NH	н	CF3	Н	Н	Н
1747	3	NHCH 2CH2NH	н	CF3	H	H	COCH 3
1748	3	NHCH 2CH2NH	Н	CF ₃	Н	СН3	H
1749	3	NHCH 2CH2NH	H	CF ₃	н	СН3	сосн 3
1750	3	NHCH 2CH2NH	OH	OH .	Н	Н .	H ×
1751	3	NHCH 2CH2NH	OH-	OH	Н	Н	COCH 3
1752	3	NHCH 2CH2NH	OH	OH .	н	СНЗ	н
1753	3	NHCH 2CH2NH	OH	OΉ	н	СНЗ	COCH 3
1754	3	NHCH 2CH2NH	F	H	F	Н	Н

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EXAMPLE NO.	n	L	R116	R ¹¹⁷	R ¹¹⁸	E	P
1755	3	NHCH 2CH2NH	F	Н	F	Н	COCH 3
1756	3	NHCH 2CH2NH	F	Н	F	CH ₃	Н
1757	3	NHCH 2CH2NH	F	Н	F	CH ₃	сосн 3
1758	3	NHCH 2CH2NH	CF3	Н	CF3	Н	Н
1759	3	NHCH 2CH2NH	CF3	Н	CF3	Н	COCH 3
1760	3	NHCH 2CH2NH	CF3	Н	CF3	CH ₃	H
1761	3	NHCH 2CH2NH	CF3	н	CF3	CH ₃	COCH 3
1762	3	piperazinyl	Н	OH	Н	Н	Н
1763	3.	piperazinyl	Н	OH	н	H	COCH 3
1764	3	piperazinyl	Н	ОН	н	СН3	н
1765	3	piperazinyl	H _.	ОH	Н	CH ₃	сосн 3
1766	3	piperazinyl	н	F	н	н	Н
1767	3	piperazinyl	Н	F	Н	н	COCH 3
1768	3	piperazinyl	Н	F	н	СН3	н
1769	3	piperazinyl	H	F	Н	СН3	COCH 3
1770	3	piperazinyl	Н	CF3	H	н	н

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EXAMPLE NO.	n	L	_R 116	R117	R118	E	P
1771	3	piperazinyl	Н	CF3	Н	Н	COCH 3
1772	3	piperazinyl	Н	CF ₃	н	CH ₃	H
1773	3	piperazinyl	Н	CF3	Н	CH ₃	сосн 3
1774	3	piperazinyl	OH	OH	н	Н	Н
1775	3	piperazinyl	OH	OH .	Н	Н	COCH 3
1776	3	piperazinyl	OH	OH	Н	СН3	H
1777	3	piperazinyl	OH	OH	Н	CH ₃	COCH 3
1778	3	piperazinyl	F	Н	F	Н	Н
1779	3	piperazinyl	F	Н	F	Н	COCH 3
1780	3	piperazinyl	F	Н	F	CH ₃	Н
1781	3	piperazinyl	F	H	F	CH ₃	COCH 3
1782	3	piperazinyl	CF3	Н	CF3	Н	Н
1783	3	piperazinyl	CF3	H	CF3	Н	COCH 3
1784	3	piperazinyl	CF3	H	CF3	CH ₃	Н
1785	3	piperazinyl	CF3	Н	CF3	СН3	COCH 3
1786	4	NHNH	Н	OH	н	Н	Н
1787	4	NHNH	Н	OH	Н	Н	COCH 3

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EXAMPLE NO.	n	L	R116	R ¹¹⁷	R118	E	Þ
1788	4	NHNH	Н	OH	Н	CH ₃	Н
1789	4	NHNH	Н	OH	Н	СН3	COCH 3
1790	4	NHNH	Н	F	Н	Н	Н
1791	4	NHNH	Н	F	н	н	COCH 3
1792	4	NHNH	Н	F	Н	СНЗ	H
1793	4	NHNH	Н	F	Н	СН3	COCH 3
1794	4	NHNH	H	CF ₃	Н	н	Н
1795	4	NHNH	Н	CF ₃	H	Н	COCH 3
1796	4	NHNH	Н	CF ₃	Н	СН3	Н
1797	4	NHNH	H	CF3	Н	СН3	COCH 3
1798	4	NHNH	OH	OH	Н	Н	Н
1799	4	NHNH	OH	OH	Н	Н	COCH 3
1800	4	NHNH	OH	OH	н	СН3	
1801	4	NHNH	OH	OH	Н	CH ₃	COCH 3
1802	4	NHNH	F	Н	F	н	Н
1803	4	NHNH	F	Н	Ė	Н	COCH 3

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EXAMPLE NO.	n	L	R116	R ¹¹⁷	R118	E	P
1804	4	NHNH	F	H	F	CH3	Н
1805	4	· NHNH	F	н	F	CH ₃	COCH 3
1806	4	NHNH	CF3	H	CF ₃	H	Н
1807	4	NHNH	CF3	н	CF ₃	н	COCH 3
1808	4	NHNH	CF3	Н	CF3	СН3	Н
1809	4	NHNH	CF3	н	CF3	СНЗ	сосн 3
1810	4	NHCH 2CH2NH	н	OH	Н	H	H
1811	4	NHCH 2CH2NH	н	OH	н	Н	COCH 3
1812	4	NHCH 2CH2NH	Н	ОН	Н	CH3	H
1813	4	NHCH 2CH2NH	Н	OH	H	CH3	сосн 3
1814	4	NHCH 2CH2NH	Н	F	Н	Н	H
1815	4	NHCH 2CH2NH	Н	F .	Н	H	соснз
1816	4	NHCH 2CH2NH	н	F :	н	СН3	H
1817	4	NHCH 2CH2NH	Н	F	Н	СНЗ	сосн з
1818	4	NHCH 2CH2NH	Н	CF3	H	Н	H
1819	4	NHCH 2CH2NH	Н	CF3	Н	Н	сосн 3
1820	4	NHCH 2CH2NH	H	CF ₃	н	CH ₃	Н

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EXAMPLE NO.	n	L	R116	R ¹¹⁷	R118	E	P
*							
1821	4	NHCH 2CH2NH	н	CF3	H	СН3	COCH 3
1822	4	NHCH 2CH2NH	OH	OH	н	Н	Н
1823	4	NHCH 2CH2NH	OH	OH	Н	н	сосн 3
1824	4	NHCH 2CH2NH	OH	OH	Н	СНЗ	Н
1825	4	NHCH 2CH2NH	OH	OH	Н	СНЗ	COCH 3
1826	4	NHCH 2CH2NH	F	Н	F	Н	Н
1827	4	NHCH 2CH2NH	F	Н	F	Н	COCH 3
1828	4	NHCH 2CH2NH	F	H	F	СН3	н
1829	4	NHCH 2CH2NH	F	Н	F	CH ₃	COCH 3
1830	4	NHCH 2CH2NH	CF3	H	CF3	Н	н
1831	4	NHCH 2CH2NH	CF3	Н	CF3	H	COCH 3
1832	4	NHCH 2CH2NH	CF ₃	Н	CF3	СНЗ	Н
1833	4	NHCH 2CH2NH	CF3	Н	CF3	СН3	COCH 3
1834	4	piperazinyl	н	OH	Н	Н	н .
1835	4	piperazinyl	Н	OH	н	Н	COCH 3
1836	4	piperazinyl	Н	OH	н	СН3	н

E	KAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R118	E	P
-	1837	4	piperazinyl	Н	OH .	н	СНЗ	сосн з
	1838	4	piperazinyl	Н	F	Н	H	Н
	1839	4	piperazinyl	Н	F	Н	Н	COCH 3
	1840	4	piperazinyl	Н	F	Н	СН3	H
	1841	4	piperazinyl	Н	F	н	CH ₃	сосн 3
	1842	4	piperazinyl	Н	CF3	н	H.	Н
	1843	4	piperazinyl	Н	CF3	н	н	сосн 3
	1844	4	piperazinyl	Н	CF3	н	CH ₃	н
	1845	4	piperazinyl	Н	CF3	Н	CH ₃	сосн 3
	1846	4	piperazinyl	OH	OH	Н	Н	H
	1847	4	piperazinyl	OH	O H	Н	Н	COCH 3
	1848	4	piperazinyl	OH	OH	н	СН3	Ĥ
	1849	4	piperazinyl	OH	OH	Н	СН3	COCH 3
	1850	4	piperazinyl	F	Н	F	Н	н
	1851	4	piperazinyl	F	Н	F	H	COCH 3
	1852	4	piperazinyl	F ·	н .	F	СНЗ	Н
	1853	4	piperazinyl	F	Н	F	СН3	COCH 3

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EXAMPLE NO.	n	L	R ¹¹⁶	R117	R118	E	P
1854	4	piperazinyl	CF ₃	H	CF ₃	Н	Н
1855	4	piperazinyl	CF3	Н	CF ₃	Н	сосн 3
1856	4	piperazinyl	CF3	Н	CF ₃	СН3	н
1857	4	piperazinyl	CF3	Н	CF3	СН3	СОСН 3

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BIOLOGICAL EVALUATION

Conjugates of the invention were evaluated biologically by in vitro and in vivo assays to determine the ability of the conjugates to selectively inhibit renal sympathetic nerve activity and lower blood pressure. Three classes of conjugates of the invention were evaluated for their ability to inhibit the enzymes of the catecholamine cascade selectively within the kidney. These inhibitor conjugates variously inhibit tyrosine hydroxylase, dopadecarboxylase and dopamine- β -hydroxylase in order to interfere ultimately with the synthesis of norepinephrine in the kidney.

Assays I and II evaluate in vivo the acute and chronic effects of Ex. #3 conjugate (a tyrosine hydroxylase inhibitor conjugated with N-acetyl-γ-glutamyl) in rats.

Assay III evaluates the chronic effects of Ex. #464 conjugate (a dopa-decarboxylase inhibitor conjugated with N-acetyl-γ-glutamyl) in rats.

Assay IV and V describes in vitro experiments performed to determine if the Ex. #859 conjugate was capable of being specifically metabolized by enzymes known to be abundant in the kidney. In Assay IV, the Ex. #859 conjugate was incubated with either rat kidney homogenate or a solution containing purified kidney enzymes to characterize resulting metabolites. In Assay V, experiments were performed to determine the potency of the Ex. #858 and Ex. #859 conjugates and potential metabolites as inhibitors of purified dopamine- β -hydroxylase.

Assays VI through IX describe in vivo experiments performed to characterize and compare the effects of fusaric acid and various conjugates of fusaric acid (Ex. #859, Ex. #861 and Ex. #863) on spontaneously hypertensive rats (SHR) by

acute administration i.v. and i.d. and by chronic administration i.v. Assay X describes analysis of catecholamine levels in tissue from rats used in the chronic administration experiment of Assay VIII. Assays XI and XII describe in vivo experiments in dogs to determine the renal and mean arterial pressure effects of fusaric acid and Ex. #859 conjugate. Assay XIII describes mechanisms of the antihypertensive response to Ex. #859 conjugate, Assay XIV describes the antihypertensive efficacy of Ex. #859 conjugate in a second species (DOCA hypertensive micropig).

Assay I: Acute In Vivo Effects of Ex. #3 Conjugate

Sprague-Dawley rats were anesthetized with inactin (100 mg/kg, i.p.) and catheters were implanted into 15 a carotid artery for measurement of mean arterial pressure (Gould model 3800 chart recorder; Statham pressure transducer model no. P23DB) and into a jugular vein for compound administrations (i.v.). In addition, a flow probe was implanted around the left renal artery for measurement 20 of renal blood flow using Carolina Medical Electronics flow probes. Rats were allowed 60 min to stabilize before 10 minutes of control recordings of mean arterial pressure and renal blood flow were obtained. Control measurements were followed by intravenous injection of Ex. #3 conjugate and 25 saline vehicle. As shown in Table XVIII and in Figs. 1 and 2, the Ex. #3 conjugate had no acute effects on mean arterial pressure (MAP), but increased renal blood flow (RBF).

TABLE XVIII

Acute In Vivo Effects of Ex. #3 Conjugate

5		Tir	ne After I	njection	(min)	• •
		Zero	15	30	45	60_
10		Yel	nicle (0.5	ml 0.9% 1	NaCli.v.)	· · · ·
	MAP (mm Hg)	78	76	75	80	82
	RBF (ml/min)	4.9	4.5	4.2	4.6	4.7
15		Ex.#	3 Conjugat	te (100 mg	/kg i.v.)	
	MAP (mm Hg)	76 <u>±</u> 5	77 <u>±</u> 5	73 <u>±</u> 4	70 <u>±</u> 2	71 <u>+</u> 6
	RBF (ml/min)	4.8±0.8	7.1 ± 0.1	6.2 ± 0.3	5.9 ± 0.1	5.9 <u>+</u> 0.1

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Assav II: Chronic In Vivo Effects of Ex. #3 Conjugate

The Ex. #3 conjugate and saline vehicle were
infused continuously for four days in spontaneously
hypertensive rats. Mean arterial pressure was measured
(Gould Chart Recorder, model 3800; Statham P23Db pressure
transducer) via an indwelling femoral artery catheter
between 10:00 a.m. and 2:00 p.m. each day. The Ex. #3
conjugate was infused at 5 mg/hr and the saline vehicle was
infused at 300 μL/hr. via a jugular vein catheter with a
Harvard infusion pump. Results are shown in Table XIX.

TABLE XIX

Chronic In Vivo Effects of Ex. #3 Conjugate

5			Time A	fter Inje	ection (d	days)
		Zero	1	2	3	4
10			Vehicle	(300 µL/	hr)	
	MAP (mm Hg)	181 <u>+</u> 8	172±6	170±7	174 <u>+</u> 6	182 <u>+</u> 3
15			Ex. #3 (Conjugate	(5 mg/)	nr)
_3	MAP (mm Hg)	164 <u>±</u> 3	175±5	174 <u>+</u> 5	172 <u>+</u> 2	N.A.

20 Assay III: Chronic In Vivo Effects of Ex. #464 Conjugate

The Ex. #464 conjugate and saline vehicle were infused continuously for four days in spontaneously hypertensive rats. Mean arterial pressure was measured (Gould Chart Recorder, model 3800; Statham P23Db pressure transducer) via an indwelling femoral artery catheter between 10:00 a.m. and 2:00 p.m. each day. The Ex. #464 conjugate was infused at 10 mg/hr and the saline vehicle was infused at 300 µL/hr. As shown in Table XX and in Fig. 3, mean arterial pressure was lowered significantly over the four-day period.

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<u>TABLE XX</u>

Chronic In Vivo Effects of Ex. #464 Conjugate

5			Time A	fter Inje	ection (d	ays)	
	· ·	Zero	1	2 .	3	4	;.
			Vehicle	(300 µL	/hr)		
10	MAP (mm Hg)	181±8	172±6	170±7	174 <u>+</u> 6	182±3	
			Ex. #46	54 Conjuga	ate (10 m	ig/hr)	
15	MAP (mm Hg)	179 <u>±</u> 6	169 <u>±</u> 5	161 <u>±</u> 4	163 <u>±</u> 5	159 <u>+</u> 8	

20 Assay IV: In Vitro Evaluation of Enzyme Metabolism Effects of Ex. #859 Conjugate

A freshly excised rat kidney was homogenized in 10 ml cold buffer (100 mM Tris, 15mM glycylglycine, pH 7.4) with a Polytron Tissue Homogenizer (Brinkmann). The resulting suspension, diluted with buffer, was incubated in the presence of the Ex. #859 conjugate at 37°C. At various times aliquots were removed, deproteinized with an equal volume of cold trichloroacetic acid (25%) and centrifuged. The supernatant was injected onto a C-18 reverse-phase HPLC column and eluted isocratically with a mixture of acetonitrile and water (20:80 v/v) containing trifluoroacetic acid (0.05%). Eluted compounds were monitored by absorbance at 254 nm and compared to standards run under identical conditions. In the assay using pure kidney enzyme homogenate,, the Ex. #859 conjugate was also

incubated under the same conditions as described except that 5 mg of gamma-glutamyl transpeptidase (Sigma, 23 units/mg) and 10 mg of acylase I (Sigma, 4800 units/mg) were added in place of the homogenate. Analysis by HPLC was performed in a manner identical to that used for the kidney homogenate experiment. Following incubation of the Ex. #859 conjugate with kidney homogenate, there was a linear increase in the amount of fusaric acid liberated, as shown in Figure 4. No fusaric acid hydrazide or gammaglutamyl fusaric acid hydrazide was observed; nor was any metabolism observed in the buffer control incubations. These data (Table XXI, Figure 4) show that renal tissue is able to metabolize the Ex. #859 conjugate to fusaric acid, which then remains stable under these conditions. Data from experiments using the purified enzymes show results similar to those seen for the kidney homogenate experiment, with only fusaric acid and the unreacted compound being present (see Table XXII, Figure 5).

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TABLE XXI

	Formation of Fusaric Acid From the Ex. #859
5	Conjugate Incubated with Kidney Homogenate

	Time (hrs	s.) :	0.00	0.17	1.25	17.00	41.00
10							
	Fusaric Acid (µg/	/m1\•	0.00	0 27	0.57	2.37	5.94
	ACIG (µg)	· 1112/ •	0.00	0.27	· · · ·		

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TABLE XXII

Formation of Fusaric Acid From Ex. #859 Conjugate Incubated with Purified Transpeptidase and Acylase

	Time (hrs.) :	3	24	72	96	120
25	Fusaric Acid (µg/ml): @ pH 7.4	0.00	2.56	12.15	15.44	18.75
30	Fusaric Acid (µg/ml): @ pH 8.1	0.00	1.12	4.46	5.22	6.55

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Assay V: In Vitro Evaluation of DBH Inhibition by Ex. #859 Conjugate

In order to characterize the relative potency of 5 the Ex. #859 conjugate and its various potential metabolites as inhibitors of dopamine beta-hydroxylase (DBH; EC 1.14.17.1), the enzyme activity was determined in vitro in the presence of these compounds. DBH, purified from bovine adrenals (Sigma) was incubated at 37°C in buffer containing 20 mM dopamine as substrate. The reaction 10 was stopped by addition of 0.5 M perchloric acid. The precipitate was removed and the product of the enzyme activity (norepinephrine), contained in the clear supernatant, was analyzed by HPLC. The chromatographic 15 separation used a reversed phase C-18 column run isocratically with 0.2 M ammonium acetate (pH 5.2) as the mobile phase. The amount of norepinephrine produced by the enzyme-substrate mixture was analyzed by measuring the peak intensity (absorbance) at 280 nm for norepinephrine as it 20 was eluted at 4.5 minutes, using a photo-diode array detector. The result of adding either fusaric acid or the Ex. #859 conjugate to the incubate at various concentrations is shown in Table XXIII and Figure 6. Above concentrations of 1 uM, fusaric acid inhibits the enzyme, while at concentrations up to 100 uM the Ex. #859 conjugate 25 has no appreciable activity (Table XXIII and Figure 6). Fusaric acid and Ex. #859 and two more possible metabolites (Ex #858 and fusaric acid hydrazide) were tested at 20 uM. Only fusaric acid had significant inhibitory effects on 30 dopamine- β -hydroxylase activity (Table XXIV and Figure 7).

TABLE XXIII

OBH Inhibition by Fusaric Acid and the Ex. #859 Conjugate

Concentration (µM):	0.01 0.10 0.50 1.00 5.00 10.00 50.00 100.00	0.01 0.10 0.50 1.00 5.00 10.00 50.00 100.00	0.50	1.00	5.00	10.00	50.00	100.00
Norepinephrine Peak Intensity (Abs 280) in the presence of Fusaric Acid:	0.59	0.59 0.59 0.60 0.53 0.25 0.14 0.00	09.0	0.53	0.25	0.14	0.00	0.00
Norepinephrine Peak Intensity (Abs 280) in the presence of Ex. #859 Conjugate		0.51		0.52		0.61		0.53

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TABLE XXIV

DBH Inhibition by Fusaric Acid, Ex. #859 Conjugate and Various Potential Metabolites

10	Test	Ex.	Ex.	Fusaric Acid	Fusaric
	Compound (20μM):	#859	#858	Hydrazide	Acid
	% Inhibition :	1.5	0.0	13.8	75.4

Assay VI: Acute In Vivo Effects of Ex. #859 and Ex. #863 Conjugates

Spontaneously hypertensive rats were anesthetized with inactin (100 mg/kg, i.p.) and catheters were implanted 20 into a carotid artery for measurement of mean arterial pressure (Gould model 3800 chart recorder; Statham pressure transducer model no. P23DB) and into a jugular vein for compound administrations (i.v. or i.d.). In addition, a flow probe was implanted around the left renal artery for 25 measurement of renal blood flow using pulsed Doppler flowmetry. Rats were allowed 60 min to stabilize before 10 minutes of control recordings of mean arterial pressure and renal blood flow were obtained. Control measurements were followed by intravenous injection of 50 mg/kg of fusaric acid 30 or the Ex. #859 conjugate. As shown in Figures 8 and 9 and Table XXV, fusaric acid (a systemic dopamine- β -hydroxylase inhibitor) decreased mean arterial pressure and increased renal blood flow throughout the 60 minute post-injection observation period. In sharp contrast, the Ex. #859 conjugate 35 had no acute effects on mean arterial pressure, but increased

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renal blood flow to a greater degree than fusaric acid (Table XXV and Figures 8 and 9). Similar results were found when these compounds were administered through a catheter implanted into the duodenum (i.d.). The Ex. #859 conjugate had no effect on mean arterial pressure at a dose of 100 mg/kg (n=4) during a 60 minute observation period. Renal blood flow (n=4) was unchanged 15 minutes after injection of the Ex. #859 conjugate but increased from 1.1 KHz (control period) to 3.5 KHz at 30 minutes postinjection. Renal blood flow remained at this level for the following 30 minute observation period. These data indicate that the Ex. #859 conjugate is active and displays renal selectivity whether administered i.d. or i.v. Results for Ex. #863 conjugate were similar to Ex. #859 and are shown in Table XXVI: Ex. #863 had no effect on mean arterial pressure, but increased renal blood flow, indicating renal selectivity.

TABLE XXV

20 Acute Effects of Fusaric Acid and Ex. #859 conjugate on Blood Pressure and Renal Blood Flow

			Time (min)					
		Zero	15	30	45	60		
25								
		Fusaric Acid (50mg/kg i.v.)						
	MAP (mm Hg)	155	111	106	103	99		
	RBF (KHz)	2.5	3.1	3.2	3.4	3.9		
30								
			Ex. #859	Conjugate	(50 mg/kg	i.v.)		
		•						
	MAP (mm Hg)	156	163	164	157	159		
35	RBF (KHz)	2.4	3.8	4.0	4.6	4.8		

Table XXVI

Acute Effects of Ex. #863 Conjugate

5					Time (min	ıΣ	
			Zero	15	30	45	60
10	MAP RBF	(mm Hg) (KHz)	149 <u>+</u> 14 1.6±0.2	Ex. N.A. N.A.	#863 (100 r N.A. N.A.	ng/kg i.v N.A. N.A.	
							1.0_0.0

15 N.A. = Not Available

Assay VII: Comparison of Fusaric Acid. Fusaric Acid Hydrazide

20 and Ex. #859 Conjugate on Arterial Pressure in Spontaneously
Hypertensive Rats (SHR)

Mean arterial pressure effects of fusaric acid hydrazide (100 mg/kg, i.v.), fusaric acid (100 mg/kg, i.v.) and Ex. #859 conjugate (250 mg/kg, i.v.) are shown in Table XXVII during a vehicle control period and 60 min post-injection of compound in anesthetized SHR. Rats were prepared as described above, minus the renal artery flow probe.

Table XXVII

Acute Effects of Fusaric Acid, Fusaric Acid Hydrazide and Ex. #859 Conjugate on Blood Pressure

5			
	COMPOUND	ZERO	60 MIN
	Fusaric Acid (n=4)	164 ± 10 mmHg	110 ± 21 mmHg
10	Fusaric Acid Hydrazide (n=4)	159 ± 8 mmHg	104 ± 13 mmHg
	Ex. #859 Conjugate (n=4)	151 ± 9 mmHg	146 ± 15 mmHg

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The data show that the hypotensive effects of the fusaric acid hydrazide is similar to fusaric acid. The Ex. #859 conjugate had no effect on mean arterial pressure (Table XXV, XXVII and Figure 8). The observation of no effect on mean arterial blood pressure confirms the expectation that the Ex. #859 conjugate does not act systemically.

25 Assay VIII: Chronic In Vivo Effects of Ex. #859 Conjugate

The Ex. #859 conjugate and saline vehicle were infused continuously for 5 days in SHR. Mean arterial pressure was measured (Gould Chart Recorder, model 3800; Statham P23Db pressure transducer) via an indwelling femoral artery catheter between 10:00 a.m. and 2:00 p.m. each day. The Ex. #859 conjugate (5 mg/hr), fusaric acid (2.5 mg/hr), and saline (100 µl/hr) were infused via a jugular vein catheter with a Harvard infusion pump. Compared to the control vehicle fusaric acid and the Ex. #859 conjugate lowered mean arterial pressure similarly. Mean arterial pressure did not change in the

saline vehicle group. Results are shown in Table XXVIII.and Figure 10.

TABLE XXVIII

Chronic Effects of Fusaric Acid and Ex. #859 Conjugate on Blood Pressure

5

			Time (days)				
		Zero	1	2	3	4	5
							
10				Vehicle	(25 μ፲/)։	ir)	
	MAP (mm Hg)	139 <u>+</u> 2	139±4	143 <u>+</u> 4	146 <u>+</u> 4	145 <u>+</u> 7	146 <u>+</u> 4
15			· E	usaric A	cid (2.5	ma/hr)	
	MAP (mm Hg)	148 <u>+</u> 6	118 <u>±</u> 5	114 <u>+</u> 7	122 <u>+</u> 5	114 <u>+</u> 6	114 <u>+</u> 3
	(SE)						•
20			Ex.	#859 Cor	njugate (5 mg/hr)	
	MAP (mm Hg)	146 <u>±</u> 5	122 <u>±</u> 9	115 <u>+</u> 9	119 <u>+</u> 11	121 <u>+</u> 7	115 <u>+</u> 8

Assay IX: Chronic In Vivo Effects of Ex. #861 and Ex. #863 Conjugates

The conjugates of Ex. #861 and #863 and saline 5 vehicle were infused continuously for 4 days in spontaneously hypertensive rats. Mean arterial pressure was measured (Gould Chart Recorder, model 3800; Statham P23Db pressure transducer) via an indwelling femoral artery catheter between 10:00 a.m. and 2:00 p.m. each day. The Ex. #861 and Ex. #863 conjugates were infused at 5 mg/hr and the saline vehicle was infused at 10 100 μ l/hr via a jugular vein catheter with a Harvard infusion pump. Results are shown in Table XXIX. The Ex. #863 conjugate lowered mean arterial pressure as shown in Fig. 11. Mean arterial pressure did not change for the Ex. #861 conjugate and the saline vehicle group (Table XXIX). It is 15 believed that at a higher dose of the Ex. #861 conjugate, blood pressure lowering effects would be observed.

TABLE XXIX

Chronic Effects of Ex. #861 and Ex. #863 Conjugates

on Blood Pressure

				Time (days	3)	
25		Zero	1	2	3	4
						
	Vehicle	171 <u>±</u> 6	172 <u>+</u> 6	164 <u>+</u> 6	169 <u>±</u> 4	162 <u>+</u> 4
	Ex. #861	177 <u>+</u> 3	173 <u>±</u> 3	172 <u>+</u> 4	172 <u>+</u> 3	163 <u>±</u> 9
30	Ex. #863	177±5	152 <u>±</u> 6	146 <u>+</u> 7	142 <u>+</u> 7	154 <u>+</u> 7

Assay X: Catecholamine Analysis of Tissue from Rats Treated with Ex. #859 Conjugate

In order to evaluate the renal selectivity of DBH inhibition by the Ex. #859 conjugate, the catecholamine 5 levels of heart and kidneys, both of which have been shown to be highly sensitive to DBH inhibition [Racz, K. et al., Europ. J. Pharmacol., 109, 1 (1985)], were measured following chronic infusion of the Ex. #859 conjugate, 10 fusaric acid and saline vehicle in rats. Following 5 days of infusion, the kidney was exposed through a small flank incision, made in the anesthetized rat, and the renal artery and vein were ligated. Following this the kidney was rapidly excised distal to the ligation and frozen in 15 liquid nitrogen. Similarly, the heart was excised and frozen subsequent to the removal of both kidneys. The frozen tissues were stored in closed containers at -80°C. Tissue samples were thawed on ice and their weight recorded prior to being placed in a flat bottom tube. The cold extraction solvent (2 ml/g tissue) was then added and the 20 sample was homogenized with a Polytron. Extraction Solvent: 0.1 M perchloric acid (3 ml of 70% PCA to 500 ml); 0.4 mM Na metabisulphite (38 mg/500 ml). The volume was then measured and 0.05 ml of a 1 uM/L solution of dihydroxybenzylamine (DHBA) in extraction solvent was added 25 for every 0.95 ml of homogenate to yield a 50 nM/L internal standard concentration. The homogenate was then mixed and centrifuged at 4°C, 3000 rpm for 35 minutes. A 2 ml aliquot of the supernatant was then neutralized by adding 0.5 ml of 2 M Tris, pH 8.8 and mixing. The sample was then placed on 30 an alumina column (40 mg, Spe-ed CAT cartridge; Applied Separations; Bethlehem, PA) and the catecholamines were bound, washed and eluted using a vacuum manifold system (Adsorbex SPU, EM Science, Cherry Hill, NJ) operating at 35 ca. 4 ml/min. until the column was dry. Washes of 1 ml H20. - 0.5 ml MeOH - 1 ml H₂0 were followed by elution with 1 ml

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of extraction solvent. A 200 μ l sample of the eluant was injected onto a C-18 reversed phase analytical HPLC column, 5 um, 4.6 mm x 250 mm (e.g., Beckman #235335, LKB 2134-630 Spherisorb ODS-2) and eluted with a recycled mobile phase run at ambient temperature and a flow rate of 0.5 ml/min (ca. 75 bar).

Mobile Phase: 0.02 M Na₂HP0 $_4$ in 75/25(v/v) H₂0/MeOH 0.007% SDS pH 3.5 (conc. H₃P0 $_4$). The separated catecholamines were detected with a LKB 2143

electrochemical detector at a potential setting of 500 mV using a teflon flow cell spacer of 2.2 µl and a time constant of 2 sec. Peak heights were measured and recorded along with the chromatogram tracing using a Spectra-Physics 4270 integrator. Sample runs were preceded by injection of

a mixture of calibration standards (200 ul) containing 50 nM/L of epinephrine (Epi), norepinephrine (NE), dopamine (DA), and DHBA in extraction solvent. The peak heights for each sample run were corrected by dividing the peak height of the DHBA in the standard by the peak height of the DHBA

in each sample. The resulting factor (calculated for each sample) was used to correct for losses due to dilution, non-specific binding to the tissue precipitate, incomplete elution, etc. Concentrations were calculated by multiplying the peak heights for Epi, NE and DA by that samples correction factor and then dividing this value by

samples correction factor and then dividing this value by the peak height of the respective standard. When this number is multiplied by the concentration of the standard (in this case 50 nM/L) the concentration of the catecholamine in the homogenate is obtained. This value is

multiplied by the volume of the homogenate (determined previously) to get the total catecholamine content of the tissue expressed in moles/g tissue. The resolution and retention times for a mixture of standards run under the conditions described in the previous section are shown in Table XXX.

TABLE XXX

	Retention Time (min.)		Compound
5	12.10		3,4-dihydroxylphenylacetic acid (DOPAC)
	18.24		norepinephrine (NE)
21.82	•	epinephrine (Epi)	
	23.19		homovanillic acid (HVA)
15	30.56		dihydroxybenzylamine (DHBA)
	42.58		dopamine (DA)

infusion.

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The linear response to various standards run over a 100 fold concentration range was excellent with values for both the correlation coefficient (r) and the coefficient of determination (r-squared) being >.9999 for 5 all standards, while the rank correlation (Spearman's rho) was 1.0. To confirm the precision and accuracy of the values, tissue analysis was performed on a control group of Sprague-Dawley rats. The cumulative results are within the range of values reported in the literature [(e.g. Racz, K. 10 et al, J. Cardiovasc. Pharmacol., 8, 676 (1986)]. precision in the efficiency of extraction measured by the addition of an internal standard (DHBA) was also excellent with a fractional efficiency of 0.779(SE=.066) for the kidney extraction and 0.771(SE=.083) for the heart 15 extracts. Relative to vehicle administration, both the Ex. #859 conjugate and fusaric acid decreased kidney norepinephrine concentration; however, only fusaric acid decreased heart norepinephrine concentration (see Table XXXI and Figures 12 and 13). These data indicate that the Ex. #859 conjugate is renal selective with chronic

TABLE XXXI

Effect of Fusaric Acid and Ex. #859 conjugate on Tissue Norepinephrine Concentration Following 5 Days of Infusion

Kidney Heart Tissue: Vehicle (25 μL/hr) 10 2,248 (164) 889 (72) Norepinephrine: (pMol/g) (SD) Fusaric Acid (2.5 mg/hr) 15 Norepinephrine: 519 (42) 862 (147) (pMol/g) (SD) Ex. #859 Conjugate (5 mg/hr) 20 Norepinephrine: 589 (54) 2,444 (534) (pMol/g) (SD)

Assay XI: Intrarenal Administration of Fusaric Acid in Anesthetized Dogs

In one anesthetized dog, bolus doses of fusaric acid (0.1-5.0 mg/kg) were administered into the renal artery. Mean arterial pressure (MAP), renal blood flow (RBF) and urinary sodium excretion (UNaV) were measured. Bolus intrarenal injection of isotonic saline or 0.1 mg/kg of fusaric acid had no effect on any measure; however, 0.5, 1.0, and 5.0 mg/kg fusaric acid caused dose-related increases in renal blood flow, but had no significant effect on mean arterial pressure or urinary sodium excretion (see Table XXXII).

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TABLE XXXII

Effect of Intrarenal Injection of Fusaric Acid on Blood Pressure, Sodium Excretion and Renal Blood Flow in the Dog

	Dose (mg/kg):	Saline	0.1	0.5	1.0	5.0
25	Δ RBF (ml/min):	0	0	+46	+58	+132
	U _{Na} V(μEq/min):	42.8	21.2	23.8	21.1	34.8
	MAP (mm Hg):	136	136	136	138	140

Similar results were also found in a second experiment where non-depressor doses of fusaric acid were infused into the renal arteries of two dogs (see Table XXXIII).

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TABLE XXXIII

Effect of Intrarenal Infusion of Fusaric Acid on Blood Pressure, Sodium Excretion and Renal Blood Flow in the Dog

	Infusion:	Dog #1 Fusaric Acid			Dog #2 . Fusaric Acid		
15		Saline	(1.25 mg/kg/min)	Saline	(0.75mg/kg/min)		
	Δ RBF (ml/min):	140	240	236	315		
20	U _{Na} V(μEqlmin):	95	82	. 44	13		
	MAP (mm Hg):	136	136	140	148		

These data indicate that intrarenal

25 administration of fusaric acid increases renal blood flow
in anesthetized dogs without altering systemic mean
arterial pressure.

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Assay XII: Acute In Vivo Effects of Ex. #859 Conjugate

This experiment was run to determine the renal selectivity of conjugate of the invention in dogs. Male 5 mongrel dogs (15-20 kg/ n=8; Antech, Inc., Barnhard, MO) were anesthetized with sodium pentobarbital (30 mg/kg as i.v. bolus, and 4-6 mg/kg/hr infusion) and catheters were placed in the femoral veins for compound injection or pentobarbital infusion, and the femoral artery for arterial pressure recording. An electromagnetic flow probe (Carolina Medical Electronics, Inc., King, NC) was placed around the left renal artery for measurement of renal blood flow. Renal blood flow and arterial pressure were recorded on a Gould chart recorder. After surgery, 20-30 minutes were allowed for variables to stabilize. Then a 20 minute control measurement was followed by injection of Ex. #859 conjugate at doses of 20 and 60 mg/kg, i.v., to two different groups of dogs. Variables were monitored for the next three hours. Results are shown in Table XXXIV and Figures 14 and 15.

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TABLE XXXIV

Renal Selectivity of Ex. #859 Conjugate in Dogs

J	Time Arter Injection of Da. Hos	2 CONJUGUEC
		•

		Zero	1 Hour	2 Hour	3 Hour	
	Mean Arterial		· · · · · · · · · · · · · · · · · · ·			
.0	Pressure (mmHg)					
	7 mg/kg	114 <u>+</u> 6	116 <u>±</u> 5	113 <u>+</u> 4	114 <u>+</u> 4	•
	20 mg/kg	120 <u>+</u> 3	124±2	125 <u>±</u> 3	125 <u>+</u> 4	
•	60 mg/kg	123±3	124±1	126±3	120 <u>±</u> 4	٠.,
	Vehicle	115±4	114±3	115±4	114±3	
.5			•			٠.
	Renal Blood					
	Flow (ml/min)		•	·		
	7 mg/kg	92±5	92±5	111±14	118±23	
0	20 mg/kg	88±11	107±14	122±20	126±24	: •
	60 mg/kg	131±21	145±21	168±28	176±32	•
	Vehicle	87 <u>+</u> 7	89±5	92±4	92 <u>+</u> 4	

Assav XIII: Acute In Vivo Effects of Ex. #859 Conjugate

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This experiment was run to determine the roles of the renal sympathetic nerves and dopamine in the antihypertensive response to Ex. #859. For renal blood flow experiments, male SHR (11-13 weeks of age; Harlan Sprague-Dawley, Inc., Indianapolis, IN) were anesthetized (Inactin, 100 mg/kg, i.p.), catheters were implanted in a jugular vein and carotid artery, and an electromagnetic flow probe (Carolina Medical Electronics, Inc., King, NC) was placed on the left renal artery. Care was taken not to damage the renal nerves. A tracheal catheter maintained airway patency. The SHR were placed on a heated pad to maintain normal body

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temperature (Harvard Apparatus, South Natick, MA). group of SHR (n=6) surgical renal denervation was performed (prior to implanting the flow probe) through a left flank incision by surgically stripping the renal artery and vein of adventitia and cutting all visible renal nerve bundles under a dissection microscope (X25) and coating the vessels with a solution of 10% phenol in 95% ethanol, as previously described (9,10). In a second group of SHR (n=6) bulbocapnine (a dopamine receptor antagonist) was infused at 100 $\mu g/kg/min$ starting 30 minutes prior to injection of Ex. #859 (50 mg/kg, i.v.) and continued for the duration of the study. In a third group of SHR (n=6) Ex. #859 (50 mg/kg, i.v.) was administered alone. In a final group of SHR (n=6) vehicle (0.9% NaCl) was administered. SHR were allowed 60 minutes for stabilization after surgery. After the stabilization period, 15 minutes of control mean arterial pressure and renal blood flow were obtained. Mean arterial pressure and renal blood flow were recorded for one hour.

20 For antihypertensive experiments, male SHR (11-13 weeks of age; Harlan Sprague-Dawley, Inc.; Indianapolis, IN) were habituated for 3-4 days in individual experimental cages, which became their home cages for the duration of the study. Five to seven days before experimentation, SHR were anesthetized with chloral hydrate (400 mg/kg; Sigma Chemical 25 Co., St. Louis, MO) and catheters were implanted into a femoral artery and vein. The catheters were led to the back of the neck, exteriorized, and channeled through a tether and swivel system (Alice King Chatham, Los Angeles, CA). Surgical renal denervation was performed as above. SHR that did not 30 resume normal food and water consumption were omitted from the study. Mean arterial pressure was measured via a pressure transducer (Model P23Db, Statham, Oxnard, CA) and displayed on a chart recorder (Gould, model 3800, Cleveland, OH). In 35 separate groups of conscious SHR, Ex. #859 (5 mg/kg/hr, n=6) was infused alone, Ex. #859 (5 mg/kg/hr, n=6) was coinfused

with bulbocapnine (100 μ g/kg/min), or Ex. #859 (10 mg/kg/hr, n=6) was infused 5-7 days after surgical renal denervation. Surgical renal denervation was performed as described above. After a one hour control measure of mean arterial pressure, compounds were infused for four hours and mean arterial pressure was measured continuously.

In anesthetized SHR, mean arterial pressure was not changed in any group (Table XXXV). Similarly, vehicle had no effect on renal blood flow in anesthetized SHR (Table XXXV). Renal blood flow was increased 60 minutes after injection of Ex. #859 alone, but renal blood flow was not changed by Ex. #859 during bulbocapnine infusion or after surgical renal denervation (Table XXXV).

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In conscious SHR, continuous infusion of Ex. #859 was antihypertensive over a four hour period (Table XXXVI).

Coinfusion of Ex. #859 with bulbocapnine lowered mean arterial pressure similar to Ex. #859 alone (Table XXXVI).

Bulbocapnine alone had no effect on mean arterial pressure over the four hour period (Table XXXVI). In contrast, surgical denervation of the kidneys prevented the antihypertensive response to Ex. #859 (Table XXXVI). Renal denervation also lowered baseline mean arterial pressure relative to vehicle (Table XXXVI).

Table XXXV

Role of Dopamine and Renal Nerves on Responses to Ex. #859 Conjugate

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	Mean Arterial Pressure (mmHg)	Renal Blood	Flow (ml/min)
	Vehicle n=6		
10	Time 0 minutes	151 <u>+</u> 8	8 <u>+</u> 1
	Time 60 minutes	151 ± 6	9 ± 1
	Ex. #859 n=6		
	Time 0 minutes	149 ± 8	7 <u>+</u> 2
15	Time 60 minutes	149 ± 7	12 ± 2
	Bulbocapnine + SC-47792 n=6		
	Time 0 minutes	148 ± 7	7 ± 1
	Time 60 minutes		7 ± 1
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	Renal Denervation + SC-47792	n=6	
	Time 0 minutes	143 ± 6	6 ± 1
	Time 60 minutes	139 <u>+</u> 7	6 ± 1

Table XXXVI

Role of Dopamine and Renal Nerves on Antihypertensive Response

to Ex. #859 Conjugate

	Time (hours)	0	1	2 .	3	4
10	Vehicle (n = 6)	186 ± 8	186 ± 8 ± 8	184 ± 7	180 ± 8	179
15	Ex. $\#859 (n = 6)$	177 ± 6	172 ± 6 ± 6	170 ± 7	164 <u>+</u> 7	
	$DNX \qquad (n = 6)$	157 ± 3	155 ± 4 ± 4	53 ± 4	.150 ± 4	147
20	BULBO (n = 6)	168 <u>+</u> 8	158 ± 6 ± 5	148 ± 5	140 ± 7	140
	BULBO $(n = 6)$ 1 alone	160 ± 6 1	56 ± 7 16 ± 7	51 ± 11	159 ± 6	157

Assay XIV: Chronic In Vivo Effects of Ex. #859 Conjugate in DOCA Hypertensive Micropigs

This study examines the efficacy of Ex. #859 in

deoxycorticosterone acetate (DOCA) hypertensive micropigs
(Charles River; 6 months of age). Micropigs were made
hypertensive by implanting subcutaneously DOCA strips (100
mg/kg) under isoflurane anesthesia. Hypertension stabilizes
after one month. Mean arterial pressure was measured using a

Gould chart recorder and Statham P23dB transducers. After
one month Ex. #859 conjugate was infused for three days at
5 mg/kg/hr).

Vehicle infusion (200 ml/day) had no effect on mean arterial pressure over the three day study period Table XXXVI and Figure 16). Example #859 normalized mean arterial pressure (Table XXXVI and Figure 16).

Table XXXVI

5 Effects of Ex. #859 on Mean Arterial Pressure in DOCA
Hypertensive Micropigs

10	<u>Vehicle</u>	_Day 1	Day 2		Day 3
		115 ± 3	115 ± 4		118 ± 2
15				•	· :
	Ex. #859	151 + 4	132 + 4		.119 + 3

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Compositions of the Invention

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more conjugates described above in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The conjugates of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the conjugates of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art. The conjugates and composition may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

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For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of active ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a human may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight, may be appropriate.

35 The active ingredient may also be administered by injection as a composition wherein, for example, saline,

dextrose solutions or water may be used as a suitable carrier. A suitable daily dose is from about 0.1 to 100 mg/kg body weight injected per day in multiple doses depending on the disease being treated.

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A preferred daily dose would be from about 1 to 30 mg/kg body weight. Conjugates indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 100 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 100 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 50 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of conjugate per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of conjugate per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

The dosage regimen for treating a disease condition with the conjugates and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound employed, and thus may vary widely.

For therapeutic purposes, the conjugates of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the conjugates may be admixed with lactose, sucrose, starch powder, cellulose

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esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of conjugate in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile 10 injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The conjugates may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride solutions, and/or various buffer solutions. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. Appropriate dosages, in any given instance, of course depend upon the nature and severity of the condition treated, the route of administration, including the weight of the patient.

25 Representative carriers, diluents and adjuvants include for example, water, lactose, gelatin, starches, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, petroleum jelly, etc. The pharmaceutical compositions may be made up in a solid form such as granules, powders or suppositories or in a liquid 30 form such as solutions, suspensions or emulsions. The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional pharmaceutical adjuvants such as preservatives, 35 stabilizers, wetting agents, emulsifiers, buffers, etc.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

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WHAT IS CLAIMED IS:

- 1. A conjugate comprising a first residue and a second residue, said first and second residues connected 5 together by a cleavable bond, wherein said first residue is provided by an inhibitor compound capable of inhibiting biosynthesis of an adrenergic neurotransmitter, and wherein said second residue is capable of being cleaved from said first residue by an enzyme located predominantly in the kidney.
- Conjugate of Claim 1 wherein said first and 2. second residues are provided by precursor compounds, wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and 15 the precursor of the other of said first and second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid 20 moiety and said amino moiety.
- Conjugate of Claim 2 wherein said inhibitor 3. compound providing said first residue is selected from tyrosine hydroxylase inhibitor compounds, dopadecarboxylase inhibitor compounds, dopamine- β -hydroxylase 25 inhibitor compounds, and mimics of said inhibitor compounds.
- Conjugate of Claim 3 wherein said tyrosine hydroxylase inhibitor compound is of the formula 30

$$A = \begin{bmatrix} R^{1} \\ I \\ C \\ R^{2} \end{bmatrix}_{m} \begin{bmatrix} R^{3} & O \\ I & || \\ C - CR^{5} \\ N-R^{4} \\ H \end{bmatrix}$$

wherein each of R¹ through R³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, baloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R⁵ is selected from -OR ⁶ and

R⁷
-N wherein R⁶ is selected from hydrido, alkyl,

15 cycloalkyl, cycloalkylalkyl, aralkyl and aryl, and wherein each of R⁷ and R³ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino,

20 monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; aralkyl; wherein m is a number selected from zero through six;

wherein A is a phenyl ring of the formula

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wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano,

amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy, formyl and a substituted or unsubstituted 5- or 6-membered heterocyclic ring selected from the group consisting of pyrrol-1-yl, 2-carboxypyrrol-1-yl, imidazol-2-ylamino, indol-l-yl, carbozol9-yl, 4,5-dihydro-4-hydroxy-4trifluoro-methylthiazol-3-yl, 4-trifluoromethylthiazol-2yl, imidazol-2-yl and 4,5-dihydroimidazol-2-yl; wherein any 10 two of the ${\rm R}^{\,9}$ through ${\rm R}^{\,13}$ groups may be taken together to form a benzoheterocylic ring selected from the group consisting of indolin-5-yl, 1-(Nbenzoylcarbamimidoyl)indolin-5-yl, l-carbamimidoylindolin-15 5-yl, 1H-2-oxindol-5-yl, insol-5-yl, 2mercaptobenzimidazol-5(6)-yl, 2-aminobenzimidazol-5-(6)-yl, 2-methanesulfonamidobenzimidazol-5(6)-yl, 1H-benzoxanol-2on-6-yl, 2-aminobenzothiazol-6-yl, 2-amino-4mercaptobenzothiazol-6-yl, 2,1,3-benzothiadiazol-5-yl, 1,3dihydro-2,2-dioxo2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-20 1,3-dimethyl-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 4methyl-2(H)oxoquinolin-6-yl, quinoxalin-6-yl, 2hydroxyquinoxalin-6-yl, 2-hydroxquinoxalin-7-yl, 2,3dihydroxyquinoxalin-6-yl and 2,3-didydro-3(4H)-oxo-1,4-25 benzoxazin-7-yl; 5-hydroxy-4H-pyran-4-on-2-yl, 2hydroxypyrid-4-yl, 2-aminopyrid-4-yl, 2-carboxypyrid-4-yl or tetrazolo-[1,5-a]pyrid-7-yl; and wherein A may be selected from

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$$R^{15}$$
 R^{14} R^{18} R^{19} R^{19} R^{20} R^{20} R^{21} R^{22}

wherein each of R¹⁴ through R²⁰ is independently selected from hydrido, alkyl, hydroxy, hydroxyalkyl, alkoxy, cycloalkyl, cycloalkylalkyl, halo, haloalkyl, aryloxy, alkoxycarboxyl, aryl, aralkyl, cyano, cyanoalkyl, amino, monoalkylamino and dialkylamino, wherein each of R²¹ and R²² is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; or a pharmaceutically-acceptable salt thereof.

5. Conjugate of Claim 4 wherein said inhibitor 15 compound is of the formula

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wherein each of R^1 and R^2 is hydrido; wherein m is one; wherein R^3 is selected from alkyl, alkenyl and alkynyl; wherein R^4 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R^5 is selected from OR^6 and

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and
$$-N < R^7$$
 wherein R^6 is selected from

hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R⁷ and R³ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl,

haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R^9 through R^{13} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, alkoxycarbonyl, alkoxy, arykoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, pyrrol-1-yl 2-10 carboxypyrrol-1-yl, imidazol-2-ylamino, indol-1-yl, carbazol-9-yl, 4,5-dihydro-4-trifluoromethylthiazol-3-yl, 4-trifluoromethylthiazol-2-yl, imidazol-2-yl and 4,5dihydroimidazol-2-yl, and wherein any two of the R^9 through R¹³ groups may be taken together to form a 15 benzoheterocyclic ring selected from the group consisting of indolin-5-yl, l-(N-benzoylcarbamimidoyl)indolin-5-yl, lcarbamimidoylindolin-5-yl, lH-2oxindol-5-yl, indol-5-yl, 2mercaptobenzimidazol-5(6)yl, 2-aminobenzimidazol-5-(6)-yl, 2-methanesulfonamidobenzimidazol-5(6)-yl, lH-benzoxanol-2-20 on-6-yl, 2-aminobenzothiazol-6-yl, 2-amino-4mercaptobenzothiazol-6-yl, 2,1,3-benzothiadiazol-5-yl, 1,3dihydro-2,2-dioxo-2,1, 3-benzothiadiazol-5-yl, 1,3-dihydro-1,3-dimethyl-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 4-25 methyl-2(H)oxoquinolin-6-yl, quinoxalin-6-yl, 2hydroxyquinoxalin6-yl, 2-hydroxquinoxalin-7-yl, 2,3dihydroxyquinoxalin-6-yl and 2,3-didydro-3(4H)-oxo-1,4benzoxazin-7-yl; wherein R³ is -CH=CH₂ or -C≡=CH; wherein

R⁵ is selected from OR⁶ and -N R⁷, wherein R⁶ is selected

30 from hydrido, alkyl, hydroxy, hydroxyalkyl, alkoxy, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino; and wherein each of R⁷ and R³ independently is selected from hydrido, alkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl and

35 aralkyl; or a pharmaceutically-acceptable salt thereof.

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Conjugate of Claim 5 wherein said inhibitor
    compound is selected from the group consisting of
    4-cyanoamino-a-methylphenyalanine;
    3-carboxy-a-methylphenylalanine;
 5
    3-cyano-a-methylphenylalanine methyl ester;
    α-methyl-4-thiocarbamoylphenylalanine methyl ester;
    4-(aminomethyl)-a-methylphenylalanine;
    4-guanidino-a-methylphenylalanine;
    3-hydroxy-4-methanesulfonamido-a-methylphenylalanine;
10
    3-hydroxy-4-nitro-a-methylphenylalanine;
     4-amino-3-methanesulfonyloxy-a-methylphenylalanine;
     3-carboxymethoxy-4-nitro-a-methylphenylalanine;
    \alpha-methyl-4-amino-3-nitrophenylalanine;
    3,4-diamino-a-methylphenylalanine;
15
    α-methyl-4-(pyrrol-1-yl)phenylalanine;
     4-(2-aminoimidazol-1-yl)-a-methylphenylalanine;
     4-(imidazol-2-ylamino)-a-methylphenylalanine;
     4-(4,5-dihydro-4-hydroxy-4-trifluoromethyl-thiazol-2-yl) a-
      methylphenylalanine methyl ester;
20
     \alpha-methyl-4-(4-trifluoromethylthiazol-2-yl)phenylalanine;
     \alpha-methyl-3-(4-trifluoromethylthiazol-2-yl)-phenylalanine;
     4-(imidazol-2-yl)-a-methylphenylalanine;
     4-(4,5-dihydroimidazol-2-yl)-a-methylphenylalanine;
     3-(imidazol-2-yl)-a-methylphenylalanine;
25
     3-(4,5-dihydroimidazol-2-yl)-a-methylphenylalanine;
     4-(imidazol-2-yl)phenylalanine;
     4,5-dihydroimidazol-2-yl)phenylalanine;
     3-(imidazol-2-yl)phenylalanine;
     3-(2,3-dihydro-lH-indol-4-yl)-a-methylalanine;
30
     \alpha-methyl-3-(1H-2-oxindol-5-yl)alanine;
     3-[1-(N-benzoylcarbamimidoyl)-2,3-dihydro-lHindol-5-yl)]-a
       methylalanine;
     3-1[-carbamimidoyl-2,3-dihydro-1H-indol-5-yl-a-
     methylalanine;
35
     3-(lH-indol-5-yl)-a-methylalanine;
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3-(benzimidazol-2-thione-5-yl)-a-methylalanine;
     3-(2-aminobenzimidazol-5-yl-2-methylalanine;
     2-methyl-3-(benzoxazol-2-on-6-yl)alanine;
     3-(2-aminobenzothiazol-6-yl)-2-methylalanine;
     3-(2-amino-4-mercaptobenzothiazol-6-yl)-2-methylalanine;
     3-(2-aminobenzothiazol-6-yl)alanine;
     2-methyl-3-(2,1,3-benzothiadiazol-5-yl)alanine;
     3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)-2methylalanine-
     2,2-
10
       dioxide;
     3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)-2-methylalanine-
     2,2-
       dioxide methyl ester;
     3-(1,3-dihydrobenzo-2,1,3-thiadiaxol-5-yl)alanine 2,2-
15
     dioxide;
     3-(1,3-dihydro-1,3-dimethylbenzo-2,1,3-thiadiazol-5yl-)-2-
       methylalanine 2,2-dioxide;
     \alpha-methyl-3-[4-methyl-2(1H)-oxoquinolin-6-yl]alanine;
     3-[4-methyl-2(lH)-oxoquinolin-6-yl]alanine;
20
     2-methyl-3-(quinoxalin-6-yl)alanine;
     2-methyl-3-(2-hydroxyquinoxalin-6-yl)alanine;
     2-methyl-3-(2-hydroxyquinoxalin-7-yl)alanine;
     3-(2,3-dihydroxyquinoxalin-6-yl)-2-methylalanine;
     3-(quinoxalin-6-yl)alanine;
     3-(2,3-dihydroxyquinoxalin-6-yl)alanine;
25
     3-(1,4-benzoxazin-3-one-6-yl)-2-methylalanine;
     3-(1,4-benzoxazin-3-one-7-yl)alanine;
     3-(5-hydroxy-4H-pyran-4-on-2-yl)-2-methylalanine;
     3-(2-hydroxy-4-pyridyl)-2-methylalanine;
30
    3-(2-carboxy-4-pyridyl)-2-methylamine;
    α-methyl-4-(pyrrol-1-yl)phenylalanine;
    \alpha-ethyl-4-(pyrrol-1-yl)phenylalanine;
    α-propyl-4-(pyrrol-1-yl)phenylalanine;
    4-[2-(carboxy)pyrrol-1-yl)phenylalanine;
35
    α-methyl-4-(pyrrol-1-yl)phenylalanine;
    3-hydroxy-\alpha-methyl-4-(pyrrol-l-yl)phenylalanine;
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3-methoxy-α-methyl-4-(pyrrol-1-yl)phenylalanine;
     4-methoxy-α-methyl-3-(pyrrol-l-yl)phenylalanine;
     4-(indol-l-yl)-a-methylphenylalanine;
     4-(carbazol-9-yl)-a-methylphenylalanine;
     2-methyl-3-(2-methanesulfonylamidobenzimidazol-5-
 5
     yl) alanine;
     2-methyl-3-(2-amino-4-pyridyl)alanine;
     2-methyl-3[tetrazolo-(1,5)-a-pyrid-7-yl]alanine;
     D, L-\alpha-methyl-\beta-(4-hydroxy-3-methyl) phenylalanine;
     D, L-\alpha-methyl-\beta-(4-hydroxy-3-phenyl) phenylalanine;
10
     D, L-\alpha-methyl-\beta-(4-hydroxy-3-benzyl) phenylalanine;
     D, L-\alpha-methyl-\beta-(4-methoxy-3-cyclohexyl) phenylalanlne;
     a, b, b trimethyl-\beta-(3,4-dihydroxyphenyl)alanine;
     a, b, b trimethyl-\beta-(4-hydroxyphenyl)alanine;
     N-methyl a, b, b, trimethyl-\beta-(3,4-dihydroxphenyl) alanine;
15
     D,L a, b, b trimethyl-\beta-(3,4-dihyroxyphenyl)alanine;
     a, b, b trimethyl-\beta-(3,4-dimethoxyphenyl)alanine;
     L-\alpha-methyl-\beta-3,4-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-3, 4-dihydroxyphenylalanine;
     L-\alpha-propyl-\beta-3,4-dihydroxyphenylalanine;
20
     L-\alpha-butyl-\beta-3,4-dihydroxyphenylalanine;
     L-\alpha-methyl-\beta-2, 3-dihydroxphenylalanine;
     L-\alpha-ethyl-\beta-2, 3-dihydroxphenylalanine;
     L-\alpha-propyl-\beta-2,3-dihydroxphenylalanine;
     L-\alpha-butyl-\beta-2, 3-dihydroxphenylalanine;
25
     L-\alpha-methyl-4-chloro-2,3-dihydroxyphenylalanine;
     L-\alpha-ethyl-4-chloro-2,3-dihydroxyphenylalanine;
     L-α-propyl-4-chloro-2, 3-dihydroxyphenylalanine;
     L-\alpha-butyl-4-chloro-2,3-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-4-methyl-2,3-dihydroxyphenylalanine;
30
     L-\alpha-methyl-\beta-4-methyl-2,3-dihydroxyphenylalanine;
     L-\alpha-propyl-\beta-4-methyl-2,3-dihydroxyphenylalanine;
     L-\alpha-butyl-\beta-4-methyl-2,3-dihydroxyphenylalanine;
     L-\alpha-methyl-\beta-4-fluoro-2,3-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-4-fluoro-2,3-dihydroxyphenylalanine;
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L-\alpha-propyl-\beta-4-fluoro-2,3-dihydroxyphenylalanine;L-\alpha-butyl-
      \beta-4-fluoro-2, 3-dihydroxyphenylalanine;
      L-\alpha-methyl-\beta-4-trifluoromethyl-2,3-dihydroxyphenylalanine
      L-\alpha-ethyl-\beta-4-trifluoromethyl-2,3-dihydroxyphenylalanine
      L-\alpha-propyl-\beta-4-trifluoromethyl-2,3-dihydroxyphenylalanine
      L-\alpha-butyl-\beta-4-trifluoromethyl-2,3-dihydroxyphenylalanine
      L-\alpha-methyl-\beta-3,5-dihydroxyphenylalanine;
      L-\alpha-ethyl-\beta-3,5-dihydroxyphenylalanine;
      L-\alpha-propyl-\beta-3,5-dihydroxyphenylalanine;
10
      L-\alpha-butyl-\beta-3,5-dihydroxyphenylalanine;
      L-\alpha-methyl-\beta-4-chloro-3,5-dihydroxphenylalanine;
      L-\alpha-ethyl-\beta-4-chloro-3,5-dihydroxphenylalanine;
      L-\alpha-propyl-\beta-4-chloro-3,5-dihydroxphenylalanine;
     L-\alpha-butyl-\beta-4-chloro-3,5-dihydroxphenylalanine;
     L-\alpha-methyl-\beta-4-fluoro-3,5-dihydroxyphenylalanine;
15
     L-\alpha-ethyl-\beta-4-fluoro-3, 5-dihydroxyphenylalanine;
     L-\alpha-propyl-\beta-4-fluoro-3,5-dihydroxyphenylalanine;
     L-\alpha-butyl-\beta-4-fluoro-3,5-dihydroxyphenylalanine;
     L-\alpha-methyl-\beta-4-trifluoromethyl-3,5-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-4-trifluoromethyl-3,5-dihydroxyphenylalanine;
20
     L-\alpha-propyl-\beta-4-trifluoromethyl-3,5-dihydroxyphenylal anlne;
     L-\alpha-butyl-\beta-4-trifluoromethyl-3,5-dihydroxyphenylalanine;
     L-\alpha-methyl-2,5-dihydroxphenylalanine;
     L-\alpha-ethyl-2,5-dihydroxphenylalanine;
25
     L-\alpha-propyl-2,5-dihydroxphenylalanine;
     L-\alpha-butyl-2,5-dihydroxphenylalanine;
     L-\alpha-methyl-\beta-4-chloro-2,5-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-4-chloro-2,5-dihydroxyphenylalanine;
     L-\alpha-propyl-\beta-4-chloro-2,5-dihydroxyphenylalanine;
30
     L-\alpha-butyl-\beta-4-chloro-2,5-dihydroxyphenylalanine;
     L-\alpha-methyl-\beta-4-chloro-2,5-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-4-chloro-2, 5-dihydroxyphenylalanine;
     L-\alpha-propyl-\beta-4-chloro-2,5-dihydroxyphenylalanine;
     L-\alpha-butyl-\beta-4-chloro-2, 5-dihydroxyphenylalanine;
35
     L-\alpha-methyl-\beta-methyl-2,5-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-methyl-2,5-dihydroxyphenylalanine;
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L-\alpha-propyl-\beta-methyl-2,5-dihydroxyphenylalanine;
     L-\alpha-butyl-\beta-methyl-2,5-dihydroxyphenylalanine;
     L-\alpha-methyl-\beta-4-trifluoromethyl-2,5-dihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-4-trifluoromethyl-2,5-dihydroxyphenyl alanine;
     L-\alpha-propyl-\beta-4-trifluoromethyl-2,5-dihydroxyphenylalanlne;
     L-\alpha-butyl-\beta-4-trifluoromethyl-2,5-dihydroxyphenylalanine;
     L-\alpha-methyl-\beta-3,4,5-trihydroxyphenylalanine;
     L-\alpha-\text{ethyl}-\beta-3, 4, 5-trihydroxyphenylalanine;
     L-\alpha-propyl-\beta-3,4,5-trihydroxyphenylalanine;
     L-\alpha-butyl-\beta-3,4,5-trihydroxyphenylalanine;
10
     L-\alpha-methyl-\beta-2,3,4-trihydroxyphenylalanine;
     L-\alpha-ethyl-\beta-2,3,4-trihydroxyphenylalanine;
     L-\alpha-propyl-\beta-2,3,4-trihydroxyphenylalanine;
     L-\alpha-butyl-\beta-2, 3, 4-trihydroxyphenylalanine;
     L-\alpha-methyl-\beta-2,4,5-trihydroxyphenylalanine;
15
     L-\alpha-ethyl-\beta-2,4,5-trihydroxyphenylalanine;
     L-\alpha-propyl-\beta-2,4,5-trihydroxyphenylalanine;
     L-\alpha-butyl-\beta-2, 4, 5-trihydroxyphenylalanine;
     L-phenylalanine;
     D, L-a-methylphenylalanine;
20
     D, L-3-iodophenylalanine;
     D, L-3-iodo-a-methylphenylalanine;
     3-iodotyrosine;
     3,5-diiodotyrosine;
25
     L-a-methylphenylalanine;
     D, L-\alpha-methyl-\beta-(4-hydroxy-3-methylphenyl) alanine;
     D, L-\alpha-methyl-\beta-(4-methoxy-3-benzylphenyl) alanine;
     D, L-\alpha-methyl-\beta-(4-hydroxy-3-benzylphenyl) alanine;
     D, L-\alpha-methyl-\beta- (4-methoxy-3-cyclohexylphenyl) alanine;
     D, L-\alpha-methyl-\beta-(4-hydroxy-3-cyclohexylphenyl) alanine;
30
     D_rL-\alpha-methyl-\beta-(4-methoxy-3-methylphenyl) alanine;
     D, L-\alpha-methyl-\beta-(4-hydroxy-3-methylphenyl) alanine;
     N, O-dibenzyloxycarbonyl-D, L-\alpha-methyl-\beta- (4-hydroxy-3
        methylphenyl) alanine;
     N, O-dibenzyloxycarbonyl-D, L-\alpha-methyl-\beta- (4-hydroxy-3
35
        methylphenyl) alanine amide;
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D,L-\alpha-methyl-\beta-(4-hydroxy-3-methylphenyl) alanine amide;
      N, O-diacetyl-D, L-\alpha-methyl-\beta- (4-hydroxy-3-methyl-
      phenyl) alanine;
      D, L-N-acetyl-\alpha-methyl-\beta-(4-hydroxy-3-methylphenyl) alanine;
     L-3, 4-dihydroxy-a-methylphenylalanine;
      L-4-hydroxy-3-methoxy-a-methylphenylalanine;
      L-3,4-methylene-dioxy-a-methylphenylalanine;
      2-vinyl-2-amino-3-(2-methoxyphenyl)propionic acid;
      2-vinyl-2-amino-3-(2,5-dimethoxyphenyl)propionic acid;
     2-vinyl-2-amino-3-(2-imidazolyl)propionic acid;
10
     2-vinyl-2-amino-3-(2-methoxyphenyl)propionic acid ethyl
     ester;
     \alpha-methyl-\beta-(2,5-dimethoxyphenyl)alanine;
     \alpha-methyl-\beta-(2,5-dihydroxyphenyl) alanine;
15
     \alpha-ethyl-\beta-(2,5-dimethoxyphenyl)alanine;
     \alpha-ethyl-\beta-(2,5-dihydroxyphenyl)alanine;
     \alpha-methyl-\beta-(2,4-dimethoxyphenyl)alanine;
     \alpha-methyl-\beta-(2,4-dihydroxyphenyl)alanine;
     \alpha-ethyl-\beta-(2,4-dimethoxyphenyl)alanine;
20
     \alpha-ethyl-\beta-(2,4-dihydroxyphenyl)alanine;
     \alpha-methyl-\beta-(2,5-dimethoxyphenyl)alanine ethyl ester;
     2-ethynyl-2-amino-3-(3-indolyl)propionic acid;
     2-ethynyl-2,3-(2-methoxyphenyl)propionic acid;
     2-ethynyl-2,3-(5-hydroxyindol-3-yl)propionic acid;
25
     2-ethynyl-2-amino-3-(2,5-dimethoxyphenyl)propionic acid;
     2-ethynyl-2-amino-3-(2-imidazolyl)propionic acid;
     2-ethynyl-2-amino-3-(2-methoxyphenyl)propionic acid ethyl
     ester;
     3-carbomethoxy-3-(4-benzyloxybenzyl)-3-aminoprop-1-yne;
30
     α-ethynyltyrosine hydrochloride;
     \alpha-ethynyltyrosine;
     α-ethynyl-m-tyrosine;
     \alpha-ethynyl-\beta-(2-methoxyphenyl)alanine;
     \alpha-ethynyl-\beta-(2,5-dimethoxyphenyl)alanine; and
35
     \alpha-ethynylhistidine.
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7. Conjugate of Claim 5 wherein at least one of R^{10} , R^{11} and R^{12} is selected from hydroxy, alkoxy, aryloxy, aralkoxy and alkoxycarbonyl; or a pharmaceutically-acceptable salt thereof.

5 8. Conjugate of Claim 7 wherein said inhibitor compound is selected from the group consisting of α-methyl-3-(pyrrol-1-yl)tyrosine; α-methyl-3-(4-trifluoromethylthiazol-2-yl)tyrosine; 3-(imidazol-2-yl)-b-methyltyrosine; 10 $L-\alpha$ -methyl-m-tyrosine; $L-\alpha$ -ethyl-m-tyrosine; $L-\alpha$ -propyl-m-tyrosine; $L-\alpha$ -butyl-m-tyrosine; 15 L-α-methyl-p-chloro-m-tyrosine; $L-\alpha$ -ethyl-p-chloro-m-tyrosine; $L-\alpha$ -butyl-p-chloro-m-tyrosine; L-α-methyl-p-bromo-m-tyrosine; $L-\alpha$ -ethyl-p-bromo-m-tyrosine; L-α-butyl-p-bromo-m-tyrosine; 20 L-α-methyl-p-fluoro-m-tyrosine; L-α-methyl-p-iodo-m-tyrosine; $L-\alpha-ethyl-p-iodo-m-tyrosine;$ $L-\alpha$ -methyl-p-methyl-m-tyrosine; 25 L-a-methyl-p-ethyl-m-tyrosine; L-α-ethyl-p-ethyl-m-tyrosine; $L-\alpha-ethyl-p-methyl-m-tyrosine;$ L-α-methyl-p-butyl-m-tyrosine; L-α-methyl-p-trifluoromethyl-m-tyrosine; L-3-iodotyrosine; 30 L-3-chlorotyrosine;

L-3-chlorotyrosine;
L-3,5-diiodotyrosine;
L-a-methyltyrosine;
D,L-a-methyltyrosine;
D,L-3-iodo-a-methyltyrosine;
L-3-bromo-a-methyltyrosine;

D,L-3-bromo-a-methyltyrosine; L-3-chloro-a-methyltyrosine; D,L-3-chloro-a-methyltyrosine; and 2-vinyl-2-amino-3-(4-hydroxyphenyl)propionic acid.

5

9. Conjugate of Claim 4 wherein said inhibitor compound is of the formula

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wherein R³ is selected from alkyl, alkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein m is a number selected from zero through five, inclusive; wherein R⁵ is selected from OR⁶ and

25 $-N < \frac{R^7}{R^8}$, wherein R^6 is selected from

hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R⁷ and R³ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfinyl, arylsulfinyl and arylsulfonyl; wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl,

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cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, alkoxycarbonyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; or a pharmaceutically-acceptable salt thereof.

- 10. Conjugate of Claim 9 wherein at least one of R¹⁰, R¹¹ and R¹² is selected from hydroxy, alkoxy,
 10 aryloxy, aralkoxy and alkoxycarbonyl; or a pharmaceutically-acceptable salt thereof.
- 11. Conjugate of Claim 10 wherein said
 inhibitor compound is selected from the group consisting of
 15 methyl(+)-2-(4-hydroxyphenyl)glycinate; isopropyl and 3methyl butyl esters of (+)-2-(4-hydroxyphenyl)glycine; (+)2-(4-hydroxyphenyl)glycine; 2-(4-hydroxyphenyl)glycine;
 (+)-2-(4-methoxyphenylglycine; and (+)-2-(4-hydroxyphenyl)glycinamide.

12. Conjugate of Claim 4 wherein said inhibitor

compound is of the formula R^{14} R^{15} R^{16} R^{17} R^{18} R^{1} R^{1

wherein each of R¹ and R² is hydrido; wherein R³ is selected from alkyl, alkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein m is a number selected from zero through five, inclusive; wherein each of

R14 through R17 is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cyclo-alkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl; or a pharmaceutically-acceptable salt thereof.

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- 13. Conjugate of Claim 12 wherein said inhibitor compound is selected from the group consisting of L-a-methyltryptophan;
- D, L-5-methyltryptophan;
- 15 D,L-5-chlorotryptophan;
 - D, L-5-bromotryptophan;
 - D, L-5-iodotryptophan;
 - L-5-hydroxytryptophan;
 - D, L-5-hydroxy-a-methyltryptophan;
- 20 α-ethynyltryptophan;
 - 5-Methoxymethoxy- α -ethynyltryptophan; and
 - $5-Hydroxy-\alpha-ethynyltryptophan.$
 - 14. Conjugate of Claim 4 wherein A is
- $= N < \frac{R^{21}}{R^{22}}$, and m is a number selected from zero to three, inclusive; or a pharmaceutically-acceptable salt thereof.
- 15. Conjugate of Claim 14 wherein said inhibitor compound is selected from the group consisting of 2-vinyl-2-amino-5-aminopentanoic acid and 2-ethynyl-2-amino-5-aminopentanoic acid.
 - 16. Conjugate of Claim 4 wherein said inhibitor compound is of the formula

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wherein each of \mathbb{R}^{23} and \mathbb{R}^{24} is independently selected from 10 hydrido, hydroxy, alkyl, cycloakyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, 15 alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R²⁵ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R²⁶ through 20 R³⁵ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, 25 carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, alkoxy and formyl; wherein n is a number selected from zero to five, inclusive; or a pharmaceutically-acceptable salt thereof.

17. Conjugate of Claim 16 wherein said inhibitor compound is benzoctamine.

18. Conjugate of Claim 3 wherein said inhibitor compound is a dopa-decarboxylase inhibitor of the formula

Wherein each of ${\bf R}^{36}$ through ${\bf R}^{42}$ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, 10 aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, 15 carboxyalkoxy and formyl; wherein n is a whole number from zero through four; wherein each of R^{43} and R^{44} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, 20 cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, alkenyl, cycloalkenyl and alkynyl; and wherein any R43 and R44 substituent having a substitutable position may be further 25 substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl; with the proviso that R^{43} and R^{44} cannot both be carboxyl at the same time, with the further proviso that when R^{36} is hydrido then R^{37} cannot be carboxyl, and with the further proviso that at least one of R43 through R^{44} must be a primary or secondary amino group; or a pharmaceutically-acceptable salt thereof.

19. Conjugate of Claim 18 wherein each of R³⁶
35 through R⁴² is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl,

alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein n is a whole number from one through three; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl and alkanoyl; and wherein any R⁴³ and R⁴⁴ substitutent having a substitutable position may be further substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl; or a pharmaceutically-acceptable salt thereof.

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- Conjugate of Claim 19 wherein each of R³⁶ 20. through R⁴² is independently selected from hydrido, hydroxy, alkyl, benzyl, phenyl, alkoxy, benzyloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, 20 alkanoyl, cyanoamino, cyano, minomethyl, carboxyl, carboxyalkoxy and formyl; wherein n is one or two; wherein each of R^{43} and R^{44} is independently selected from hydrido, alkyl, benzyl, phenyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, 25 carboxyl, carboxyalkyl and alkanoyl; and wherein any R43 and R44 substituent having a substitutable position may be further substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl; or a pharmaceutically-acceptable salt 30 thereof.
- 21. Conjugate of Claim 20 wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl,

carboxyalkoxy and formyl; wherein n is one or two; wherein each of R^{43} and R^{44} is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl and carboxyalkyl; and wherein any R^{43} and R^{44} substituent having a substitutable position may be further substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxyarbonyl; or a pharmaceutically-acceptable salt thereof.

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and R⁴² is hydrido and n is one; wherein each of R³³ through R⁴² is independently selected from hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl and carboxyalkyl; and wherein any R⁴³ and R⁴⁴ substituent having a substitutable position may be further substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl; or a pharmaceutically-acceptable salt thereof.

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- 23. Conjugate of Claim 22 wherein said inhibitor compound is selected from (2,3,4-trihydroxy) benzylhydrazine; 1-(D,L-seryl-2-(2,3,4-trihydroxybenzyl) hydrazine; and 1-(3-hydroxyl-benzyl)-l-methylhydrazine.
- 24. Conjugate of Claim 21 wherein each of R^{36} and R^{37} is independently selected from hydrido, alkyl and amino and n is two; wherein each of R^{38} through R^{42} is independently selected from hydroxy, alkyl, alkoxy,

haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl and carboxyalkyl; or a pharmaceutically-acceptable salt thereof.

- 25. Conjugate of Claim 24 wherein said inhibitor compound is selected from 2-hydrazino-2-methyl-3-(3,4-dihydroxyphenyl)propionic acid; α -(monofluoromethyl)dopa; α -(difluoromethyl)dopa; and α -methyldopa.
- 26. Conjugate of Claim 3 wherein said inhibitor compound is a dopa-decarboxylase inhibitor of the formula

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wherein each of R^{45} through R^{43} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl; wherein each of R^{49} and R^{50} is independently selected from hydrido, alkyl, cycloalkyl, cycloalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl,

cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl and

- CR⁵¹ wherein R^{51} is selected from hydroxy, alkoxy, aryloxy, aralkoxy, amino, monoalkylamino and dialkylamino; with the proviso that R^{49} and R^{50} cannot both be carboxyl at the same time, and with the further proviso that at least one of R^{45} through R^{43} is a primary or secondary amino group or a carboxyl group; or a pharmaceutically-acceptable salt thereof.
- 27. Conjugate of Claim 26 wherein each of R45 through R^{43} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, 15 alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein each of \mathbf{R}^{49} and \mathbf{R}^{50} is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, 20 alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl and alkanoyl and $-\ddot{C}R^{51}$ wherein R^{51} is selected from hydroxy, alkoxy, phenoxy; benzyloxy, amino, monoalkylamino and dialkylamino; 25 or a pharmaceutically-acceptable salt thereof.
- 28. Conjugate of Claim 27 wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, benzyl, phenyl, alkoxy, benzyloxy,

 30 alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido, alkyl, benzyl, phenyl, alkoxyalkyl,

haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl and alkanoyl and

- $-CR^{51}$ wherein R^{51} is selected from hydroxy, alkoxy, amino and monoalkylamino; or a pharmaceutically-acceptable salt thereof.
- 29. Conjugate of Claim 28 wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido alkyl, amino, monoalkylamino, carboxyalkyl and
- | 15 -CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, amino and monoalkylamino; or a pharmaceutically-acceptable salt thereof.
- 30. Conjugate of Claim 29 wherein each of \mathbb{R}^{45} 20 through \mathbb{R}^{48} is independently selected from hydrido, hydroxy, alkyl, alkoxy and hydroxyalkyl; wherein each of \mathbb{R}^{49} and \mathbb{R}^{50} is independently selected from alkyl, amino, monoalkylamino, and
- -CR⁵¹ wherein R⁵¹ is selected from hydroxy, methoxy, 25 ethoxy, propoxy, butoxy, amino, methylamino and ethylamino; or a pharmaceutically-acceptable salt thereof.
- 31. Conjugate of Claim 30 wherein said inhibitor compound is selected from endo-2-amino-1,2,3,4-30 tetrahydro-1,4-ethanonaphthalene2-carboxylic acid; ethylendo-2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylate hydrochloride; exo-2-amino-1,2,3,4-tetrahydro-

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1,4-ethanonaphthalene2-carboxylic acid; and ethyl-exo-2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylate hydrochloride.
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                     Conjugate of Claim 3 wherein said inhibitor
     compound is a dopa-decarboxylase inhibitor selected from
     2,3-dibromo-4,4-bis(4-ethylphenyl)-2-butenoic acid;
     3-bromo-4-(4-methoxyphenyl)-4-oxo-2-butenoic acid;
     N-(5'-phosphopyridoxyl)-L-3,4-dihydroxyphenylalanine;
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    N-(5'-phosphopyridoxyl)-L-m-aminotyrosine;
     D, L-b-(3, 4-dihydroxyphenyl) lactate;
     D, L-b-(5-hydroxyindolyl-3) lactate;
     2,4-dihydroxy-5-(1-oxo-2-propenyl)benzoic acid;
     2,4-dimethoxy-5-[1-oxo-3-(2,3,4-trimethoxyphenyl-2
15
       propenyl]benzoic acid;
     2,4-dihydroxy-5-[1-oxo-3-(2-thienyl)-2-propenyl] benzoic
     acid;
     2,4-dihydroxy-5-[3-(4-hydroxyphenyl)-1-oxo-2-propenyl]
    benzoic
20
       acid;
     5-[3-(4-chlorophenyl)-1-oxo-2-propenyl]-2,4-dihydroxy
    benzoic
      acid;
     2,4-dihydroxy-5-(1-oxo-3-phenyl-2-propenyl)benzoic acid;
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    2,4-dimethoxy-5-[l-oxo-3-(4-pyridinyl)-2-propenyl] benzoic
    acid;
     5-[3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]-2,4 dimethoxy
      benzoic acid;
    2,4-dimethoxy-5-(1-oxo-3-phenyl-2-propenyl)benzoic acid;
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    5-[3-(2-furanyl)-l-oxo-2-propenyl]-2,4-dimethoxy benzoic
    acid;
    2,4-dimethoxy-5-[l-oxo-3-(2-thienyl)-2-propenyl] benzoic
    acid:
    2,4-dimethoxy-5-[3-(4-methoxyphenyl)-l-oxo-2-propenyl]
35
    benzoic
     acid:
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5-[3-(4-chlorophenyl)-l-oxo-2-propenyl]-2,4-dimethoxy benzoic

acid; and

5-[3-[4-(dimethylamino)phenyl]-l-oxo-2-propenyl]-2,4

5 dimethoxy

benzoic acid.

33. Conjugate of Claim 3 wherein said inhibitor compound is a dopa-decarboxylase inhibitor of the formula:

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wherein R^{52} is selected from hydrido, OR^{64} and

 $-N \stackrel{R^{65}}{\underset{R^{66}}{\sim}}$, wherein R^{64} is selected from

hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R⁶⁵ and R⁶⁶ is independently selected from hydrido, alkyl, alkanoyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl; wherein each of R⁵³, R⁵⁴ and R⁵⁷ through R⁶³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkyl, aralkyl, aryl, alkoxycarbonyl, hydroxyalkyl, balo, cyapo, amino, monoalkylamino

- 25 hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein each of R⁵⁵ and R⁵⁶ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl,
- 30 hydroxyalkyl and carboxyalkyl; wherein each of m and n is a number independently selected from zero through six, inclusive; or a pharmaceutically-acceptable salt thereof.
- 34. Conjugate of Claim 33 wherein R52 is OR^{64} 35 wherein R⁶⁴ is selected from hydrido, alkyl, cycloalkyl,

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cycloalkylalkyl, benzyl and phenyl; wherein each of R⁵³, R⁵⁴ and R⁵⁷ through R⁶³ is independently selected from hydrido, alkyl, cycloalkyl, hydroxy, alkoxy, benzyl and phenyl; wherein each of R⁵⁵ and R⁵⁶ is independently selected from hydrido, alkyl, cycloalkyl, benzyl and phenyl; wherein each of m and n is a number independently selected from zero through three, inclusive; or a pharmaceutically-acceptable salt thereof.

- 35. Conjugate of Claim 34 wherein R⁵² is OR ⁶⁴ wherein R⁶⁴ is selected from hydrido and lower alkyl; wherein each of R⁵³ through R⁵⁸ is hydrido; wherein each of R⁵⁹ through R⁶³ is independently selected from hydrido, alkyl, hydroxy and alkoxy, with the proviso that two of the R⁵⁹ through R⁶³ substituents are hydroxy; wherein each of m and n is a number independently selected from zero through two, inclusive; or a pharmaceutically-acceptable salt thereof.
- 20 36. Conjugate of Claim 35 which is 3-(3,4-dihydroxyphenyl)-2-propenoic acid.
 - 37. Conjugate of Claim 26 wherein said dopadecarboxylase inhibitor is a compound selected from aminohaloalkyl-hydroxyphenyl propionic acids; alpha-halomethyl-phenylalanine derivatives; and indole-substituted halomethylamino acids.
- 38. Conjugate of Claim 26 wherein said dopa30 decarboxylase inhibitor is a compound selected from
 isoflavone extracts from fungi and streptomyces; sulfinyl
 substituted dopa and tyrosine derivatives; hydroxycoumarin
 derivatives; l-benzylcyclobutenyl alkyl carbamate
 derivatives; aryl/thienyl-hydroxylamine derivatives; and b2-substituted-cyclohepta-pyrrol-81H-on-7-yl alanine
 derivatives.

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39. Conjugate of Claim 3 wherein said dopamine-β-hydroxylase inhibitor compound is of the formula

B C N R⁶⁹

wherein B is selected from an ethylenic moiety, an acetylenic moiety and an ethylenic or acetylenic moiety substituted with one or more radicals selected from 10 substituted or unsubstituted alkyl, aryl and heteroaryl; wherein each of R⁶⁷ and R⁶⁸ is independently selected from hydrido and alkyl; wherein R⁶⁹ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, 15 alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is a number selected from one through five; or a pharmaceutically-20 acceptable salt thereof.

- 40. Conjugate of Claim 39 wherein B is an ethylenic or an acetylenic moiety substituted with an aryl or heteroaryl radical; and wherein n is a number from one through three; or a pharmaceutically-acceptable salt thereof.
- 41. Conjugate of Claim 39 wherein B is an ethylenic or acetylenic moiety incorporating carbon atoms in the beta- and gamma-positions relative to the nitrogen atom; and wherein n is one; or a pharmaceutically-acceptable salt thereof.
- 42. Conjugate of Claim 41 wherein said
 35 ethylenic or acetylenic moiety is substituted at the gamma

carbon with an aryl or heteroaryl radical; or a pharmaceutically-acceptable salt thereof.

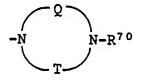
- 43. Conjugate of Claim 42 wherein said aryl
 5 radical is selected from phenyl, 2-thiophene, 3-thiophene,
 2-furanyl, 3-furanyl, oxazolyl, thiazolyl and isoxazolyl,
 any one of which radicals may be substituted with one or
 more groups selected from halo, hydroxyl, alkyl, haloalkyl,
 cyano, alkoxy, alkoxyalkyl and cycloalkyl; or a
 10 pharmaceutically-acceptable salt thereof.
- 44. Conjugate of Claim 43 wherein said aryl radical is selected from phenyl, hydroxyphenyl, 2-thiophene and 2-furanyl; and wherein each of R⁶⁷, R⁶⁸ and R⁶⁹ is hydrido; or a pharmaceutically-acceptable salt thereof.
 - 45. Conjugate of Claim 44 wherein said inhibitor compound is selected from the group consisting of 3-amino-2-(2'-thienyl)propene;
- 3-amino-2-(2'-thienyl)butene;
 3-(N-methylamino)-2-(2'-thienyl)propene;
 3-amino-2-(3'-thienyl)propene;
 3-amino-2-(2'-furanyl)propene;
 3-amino-2-(3'-furanyl)propene;
- 25 l-phenyl-3-aminopropyne; and 3-amino-2-phenylpropene.
 - 46. Conjugate of Claim 44 wherein said inhibitor compound is selected from the group consisting of
- 30 (±) 4-amino-3-phenyl-1-butyne;
 - (±) 4-amino-3-(3'-hydroxyphenyl)-1-butyne;
 - (±) 4-amino-3-(4'-hydroxyphenyl)-1-butyne;
 - (±) 4-amino-3-phenyl-1-butene;
 - (±) 4-amino-3-(3'-hydroxyphenyl)-1-butene; and
- 35 (\pm) 4-amino-3-(4'-hydroxyphenyl)-1-butene.

47. Conjugate of Claim 3 wherein said inhibitor compound is of the formula



wherein W is selected from alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl; wherein Y is selected from

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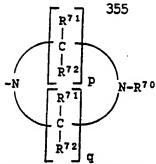


wherein R⁷⁰ is selected from hydrido, alkyl, cycloalkyl,
hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl,
aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino,
cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl,
alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each
of Q and T is one or more groups independently selected

20 from

$$\begin{bmatrix}
R^{71} \\
C \\
R^{72}
\end{bmatrix}, \quad
\begin{bmatrix}
R^{73} & R^{74} \\
C & C
\end{bmatrix}$$
and
$$\begin{bmatrix}
C & E & C
\end{bmatrix}$$

- wherein each of R⁷¹ through R⁷⁴ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; or a pharmaceutically-acceptable salt thereof.
 - 48. Conjugate of Claim 47 wherein W is heteroaryl and Y is



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wherein R⁷⁰ is selected from hydrido, alkyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyli wherein each of R⁷¹ and R⁷² is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; or a pharmaceutically-acceptable salt thereof.

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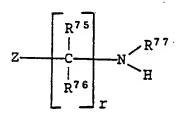
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- 49. Conjugate of Claim 48 wherein R⁷⁰ is selected from hydrido, alkyl, amino and monoalkylamino; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number indpendently selected from two through four, inclusive; or a pharmaceutically-acceptable salt thereof.
- 50. Conjugate of Claim 49 wherein R⁷⁰ is selected from hydrido, alkyl and amino; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three; or a pharmaceutically-acceptable salt thereof.
 - 51. Conjugate of Claim 50 wherein R^{70} is hydrido; wherein each of R^{71} and R^{72} is hydrido; and wherein each of p and q is two; or a pharmaceutically-acceptable salt thereof.

52. Conjugate of Claim 3 wherein said inhibitor compound is of the formula

wherein E is selected from alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkynyl, cycloalkylalkyl, aryl,

selected from



aralkyl, heterocycloalkyl and heteroaryl; wherein F is

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wherein Z is selected from 0, S and N-R⁷⁸; wherein each of R^{75} and R^{76} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, minoalkylamino, 20 dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁷⁵ and R⁷⁶ may form oxo or thio; wherein r is a number selected from zero through six, inclusive; wherein each of ${\ensuremath{\mathsf{R}}}^{77}$ and ${\ensuremath{\mathsf{R}}}^{78}$ is independently selected from hydrido, alkyl, cycloalkyl, 25 hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyli or a pharmaceutically acceptable salt thereof. 30

53. Conjugate of Claim 3 wherein said dopamine- β -hydroxylase inhibitor compound is of the formula

wherein each of R⁸² through R⁸⁵ is independently selected from hydrido, alkyl, haloalkyl, mercapto, alkylthio, cyano, alkoxy, alkoxyalkyl and cycloalkyli wherein Y is selected from oxygen atom and sulfur atom; wherein each of R⁷⁹ and R⁸⁰ is independently selected from hydrido and alkyl; wherein R⁵⁹ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein m is a number from one through six; or a pharmaceutically-acceptable salt thereof.

54. Conjugate of Claim 53 wherein each of R⁸² through R⁸⁵ is independently selected from hydrido, alkyl and haloalkyl; wherein Y is selected from oxygen atom or nitrogen atom; wherein each of R⁷⁹, R⁸⁰ and R⁸¹ is independently hydrido and alkyl; and wherein m is a number selected from one through four, inclusive; or a pharmaceutically-acceptable salt thereof.

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55. Conjugate of Claim 54 wherein said inhibitor compound is selected from aminomethyl-5-n-butylthiopicolinate; aminomethyl-5-n-butylpicolinate; 2'-aminoethyl-5-n-butylthiopicolinate; 2'-aminoethyl-5-n-butylpicolinate;

(2'-amino-1',1'-dimethyl)ethyl-5-n-butylthiopicolinate;

(2'-amino-1',1'-dimethyl)ethyl-5-n-butylpicolinate;

(2'-amino-1'-methyl)ethyl-5-n-butylthiopicolinate; (2'-amino-1'-methyl)ethyl-5-n-butylpicolinate; 3'-aminopropyl-5-n-butylthiopicolinate;

3'-aminopropyl-5-n-butylpicolinate;

(2'-amino-2'-methyl) propyl-5-n-butylthiopicolinate;

(2'-amino-2'-methyl)propyl-5-n-butylpicolinate;

5 (3'-amino-1',1'-dimethyl)propyl-5-n-butylthiopicolinate;

(3'-amino-1',1'-dimethyl) propyl-5-n-butylpicolinate;

(3'-amino-2',2'-dimethyl) propyl-5-n-butylthiopicolinate;

(3'-amino-2',2'-dimethyl)propyl-5-n-butylpicolinate;

2'-aminopropyl-5-n-butylthiopicolinate;

10 2'-aminopropyl-5-n-butylpicolinate;

4'-aminobutyl-5-n-butylthiopicolinate;

4'-amino-3'-methyl)butyl-5-n-butylthiopicolinate;

(3'-amino-3'-methyl)butyl-5-n-butylthiopicolinate; and

(3'-amino-3'-methyl)butyl-5-n-butylpicolinate.

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56. Conjugate of Claim 47 wherein said inhibitor compound is of the formula

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wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is

independently selected from hydrido, hydroxy, alkyl,
cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy,
aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl,
halo, cyano, amino, monoalkylamino, dialkylamino, carboxy,
carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl;
wherein R⁸⁶ and R⁸⁷ together may form oxo or thio; wherein
r is a number selected from zero through six, inclusive;

wherein each of R⁸⁸ and R⁸⁹ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; or a pharmaceutically-acceptable salt thereof.

- R87 and R90 through R93 is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein r is a number selected from zero through four, inclusive; wherein each of R88 and R89 is independently selected from hydrido, alkyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl; or a pharmaceutically-acceptable salt thereof.
- 58. Conjugate of Claim 57 wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein r is anumber selected from zero through three, inclusive; and wherein each of R⁸⁸ and R⁸⁹ is selected from hydrido, alkyl, amino and monoalkylamino; or a pharmaceutically-acceptable salt thereof.
- 59. Conjugate of Claim 58 wherein each of R⁹⁰

 through R⁹³ is independently selected from hydrido and alkyl; wherein each of R⁸⁶ and R⁸⁷ is hydrido; wherein r is selected from zero, one and two; wherein R⁸⁸ is selected from hydrido, alkyl and amino; and wherein R⁸⁹ is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

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- 60. Conjugate of Claim 59 wherein said inhibitor compound is 5-n-butylpicolinic acid hydrazide.
- 61. Conjugate of Claim 3 wherein said dopamine- β -hydroxylase inhibitor compound is of the formula

wherein each of R⁹⁴ through R⁹⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, aryloxy, alkoxy, alkylthio, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, amido, alkylamido, hydroxyamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, formoyl and alkoxycarbonyl; with the proviso that at least one of R⁹⁴ through R⁹⁸ is

$$-(CH_2)_t$$
 A'

wherein A' is
$$-CR^{99}$$
 or $-N < R^{101}$

wherein R⁹⁹ is selected from hydrido, alkyl, hydroxy, alkoxy, alkylthio, phenyl, phenoxy, benzyl, benzyloxy,

-OR 100 and -N R102, wherein R100 is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenyl and benzyl; wherein each of R101 and R102 is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein t is a number

selected from zero through four, inclusive; or a pharmaceutically-acceptable salt thereof.

62. Conjugate of Claim 61 wherein said 5 inhibitor compound is of the formula

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wherein each of R⁹⁵ through R⁹⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, phenyl, benzyl, alkoxy, phenoxy, benzyloxy, alkoxyalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, amido, alkylamido, hydroxyamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, carboxyl, thiocarbamoyl, aminomethyl, nitro, formoyl, formyl and alkoxycarbonyl; and wherein R¹⁰⁰ is selected from hydrido, alkyl, phenyl and benzyl; or a pharmaceutically-acceptable salt thereof.

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63. Conjugate of Claim 62 wherein said inhibitor compound is selected from 5-n-butylpicolinic acid; 5-ethylpicolinic acid; lcollnlc acId; 5-nitropicolinic acid;

5-aminopicolinic acid;

5-N-acetylaminopicolinic acid;

5-N-propionylaminopicolinic acid;
5-N-hydroxyaminopicolinic acid;

5-iodopicolinic acid;

5-bromopicolinic acid;

5-chloropicolinic acid;

5-hydroxypicolinic acid;
5-methoxypicolinic acid;

PCT/US91/00611

5-N-propoxypicolinic acid;
5-N-butoxypicolinic acid;
5-cyanopicolinic acid;
5-carboxylpicolinic acid;
5-n-butyl-4-nitropicolinic acid;
5-n-butyl-4-methoxypicolinic acid;
5-n-butyl-4-ethoxypicolinic acid;
5-n-butyl-4-aminopicolinic acid;
5-n-butyl-4-hydroxyaminopicolinic acid; and
10 5-n-butyl-4-methylpicolinic acid.

- 64. Conjugate of Claim 63 wherein said inhibitor compound is 5-n-butylpicolinic acid.
- 15 65. Conjugate of Claim 3 wherein said dopamineβ-hydroxylase inhibitor compound is of the formula

$$R^{109} = S = \begin{bmatrix} R^{106} \\ R^{107} \\ CH \end{bmatrix} = \begin{bmatrix} R^{106} \\ CH \end{bmatrix} = \begin{bmatrix} R^{1$$

20

wherein R^{105} is hydrido, hydroxy, alkyl, amino and alkoxy; wherein R^{106} is selected from hydrido, hydroxy and alkyl; wherein each of R^{107} and R^{108} is independently selected from hydrido, alkyl and phenalkyl; wherein R^{109} is selected from hydrido and O

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 $\ddot{C}-R^{110}$ with R^{110} selected from alkyl, phenyl and phenalkyl; wherein u is a number from one to three, inclusive; and wherein v is a number from zero to two, inclusive; or a pharmaceutically-acceptable salt thereof.

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66. Conjugate of Claim 65 wherein R^{105} is selected from hydroxy and lower alkoxy; wherein R^{106} is hydrido; wherein R^{107} is selected from hydrido and lower alkyl; wherein R^{108} is hydrido; wherein R^{109} is selected from hydrido and

O \parallel C-R¹¹⁰ with R¹¹⁰ selected from lower alkyl and phenyl; wherein u is two; and wherein v is a number from zero to two, inclusive; or a pharmaceutically-acceptable salt thereof.

67. Conjugate of Claim 66 wherein said inhibitor compound is of the formula

wherein R¹¹¹ is selected from hydroxy and lower alkyl; 20 wherein R¹⁰⁷ is selected from hydrido and lower alkyl; wherein R¹⁰⁹ is selected from hydrido and

O \parallel C-R¹¹⁰ with R¹¹⁰ selected from lower alkyl and phenyl and v is a number from zero to two, inclusive; or a pharmaceutically-acceptable salt thereof.

68. Conjugate of Claim 67 wherein R¹¹¹ is hydroxy; wherein R¹⁰⁷ is hydrido or methyl; wherein R¹⁰⁹ is hydrido or acetyl; and wherein n is a number from zero to two, inclusive; or a pharmaceutically-acceptable salt thereof.

- 69. Conjugate of Claim 68 wherein said inhibitor compound is 1-(3-mercapto-2-methyl-loxopropyl)-L-proline.
- 70. Conjugate of Claim 3 wherein said dopamineβ-hydroxylase inhibitor compound is of the formula

- wherein each of R¹¹² through R¹¹⁹ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, aralkyl, aryl, alkoxycarbonyl, hydroxyalkyl, halo, haloalkyl, cyano, amino, aminoalkyl, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, mercapto and alkylthio; or a pharmaceutically-acceptable salt thereof.
- 71. Conjugate of claim 70 wherein R¹¹² is selected from mercapto and alkylthio; wherein each of R¹¹³
 20 and R¹¹⁴ is independently selected from hydrido, amino, aminoalkyl, monoalkylamino, monoalkylaminoalkyl, carboxyl and carboxyalkyl; wherein each of R¹¹⁵ and R¹¹⁹ is hydrido; and wherein each of R¹¹⁶, R¹¹⁷ and R¹¹⁸ is independently selected from hydrido, hydroxy, alkyl, halo and haloalkyl; or a pharmaceutically-acceptable salt thereof.
 - 72. Conjugate of Claim 71 wherein R¹¹² is selected from amino, aminoalkyl, monoalkylamino, monoalkylaminoalkyl, carboxy and carboxyalkyl; wherein each

of R^{113} , R^{114} , R^{115} and R^{119} is hydrido; and wherein each of R^{116} , R^{117} and R^{118} is independently selected from hydrido, hydroxy, alkyl, halo and haloalkyl; or a pharmaceutically-acceptable salt thereof.

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73. Conjugate of Claim 2 wherein said precursor compound providing the second residue has a reactable acid moiety.

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74. Conjugate of Claim 73 wherein said second residue precursor compound of said conjugate is selected from a class of glutamic acid derivatives of the formula

$$\begin{array}{c} O \\ \parallel \\ C\text{-}G \\ \\ GCCH_2CH_2CH \\ \gamma \quad \beta \quad \alpha \quad N \\ \\ R^{150} \\ \end{array}$$

15

wherein each of R^{150} and R^{151} may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-OR^{152}$, $-SR^{153}$ and NR^{154} with each R^{152} , R^{153} and R^{154} is independently selected from hydrido and alkyl; with the proviso that said glutamic acid derivative is selected such that formation of the cleavable bond occurs at the carbonyl moiety attached at the gamma-position carbon of said gamma-glutamic acid derivative.

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75. Conjugate of Claim 74 wherein R^{110} wherein each G is hydroxy; wherein R^{150} is hydrido; and wherein R^{151} is selected from

-CR¹⁵⁵ wherein R¹⁵⁵ is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

- 76. Conjugate of Claim 2 wherein said first and second residues are connected through a cleavable bond provided by a linker group between said first and second residues.
- 10 77. Conjugate of Claim 76 wherein said linker group is selected from a class of diamino-terminated linker groups of the formula

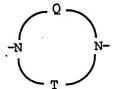
$$-N - (CH_2)_n N - N$$

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wherein each of R²⁰⁰ and R²⁰¹ may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfino, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

- 78. Conjugate of Claim 77 wherein each of R^{200} and R^{201} is hydrido; and wherein n is zero.
 - 79. Conjugate of Claim 76 wherein said linker group is selected from diamino terminal linker groups of the formula

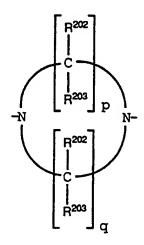


wherein each of ${\tt Q}$ and ${\tt T}$ is one or more groups independently selected from

$$\begin{array}{c|c}
 & R^{202} \\
 & C \\
 & R^{204} \\
 & C \\
 & C
\end{array}$$
and
$$\begin{array}{c|c}
 & R^{204} \\
 & C \\
 & C
\end{array}$$

wherein each of R²⁰² through R²⁰⁵ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

80. Conjugate of Claim 79 wherein said linker 15 group is of the formula



wherein each of R²⁰² and R²⁰³ is independently selected from 20 hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R^{202} and R^{203} is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R^{202} or R^{203} is attached not adjacent to a nitrogen atom.

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- 81. Conjugate of Claim 80 wherein said linker group is selected from divalent radicals wherein each of R²⁰² and R²⁰³ is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.
- 82. Conjugate of Claim 81 wherein each of R²⁰² and R²⁰³ is independently selected from hydrido, amino,
 15 monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three.
 - 83. Conjugate of Claim 82 wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two.

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84. Conjugate of Claim 76 wherein said linker group is selected from diamino terminal linker groups of the formula

$$-N = \begin{bmatrix} R^{214} & R^{216} \\ C & N \end{bmatrix}$$

$$-R^{215}$$

$$-R^{217}$$

$$-R^{217}$$

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wherein each of R²¹⁴ through R²¹⁷ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfino, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six, inclusive.

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- 85. Conjugate of Claim 84 wherein each of R²¹⁴ and R²¹⁵ is hydrido; wherein each of R²¹⁶ and R²¹⁷ is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three.
- 86. Conjugate of Claim 86 wherein each of R^{214} and R^{215} is hydrido; wherein each of R^{216} and R^{217} is independently selected from hydrido and alkyl; and wherein p is two.
 - 87. Conjugate of Claim 86 wherein each of R^{214} through R^{217} is hydrido; and wherein p is two.
- 15 Conjugate of Claim 3 selected from the group 88. consisting of 4-amino-4-carboxy-1-oxobutyl-α-methyl-L-tyrosine, methyl ester; $N-[4-(acetylamino)-4-carboxy-1-oxobutyl]-\alpha-methyl-L-tyrosine,$ 20 methyl ester; N-[4-(acetylamino)-4-carboxy-1-oxobutyl]- α -methyl-L-tyrosine; 4-amino-4-carboxy-1-oxobutyl-3-hydroxy- α -methyl-L-tyrosine, methyl ester; N-[4-(acetylamino)-4-carboxy-1-oxobuty1]-3-hydroxy- α -methyl-L-25 tyrosine, methyl ester; $N-[4-(acetylamino)-4-carboxy-1-oxobutyl]-3-hydroxy-\alpha-methyl-L$ tyrosine; L-glutamic acid, 5-{[(5-butyl-2-pyridinyl)carbonyl]hydrazide);
- N-acetyl-L-glutamic acid, 5-[(5-butyl-2-pyridinyl)
 carbonyl]hydrazide;
 N-[2-[[(5-butyl-2-pyridinyl)carbonyl]amino]ethyl]-L-glutamine;
 N^2-acetyl-N-[2-[[(5-butyl-2-pyridinyl)carbonyl]amino]ethyl]-L-glutamine;
- 2-amino-5-[4-[(5-butyl-2-pyridinyl)carbonyl]-1-piperazinyl]-5oxopentanoic acid;

2-(acetylamino)-5-(4-[(5-butyl-2-pyridinyl)carbonyl]-1-piperazinyl]-5-oxopentanoic acid; and N²-acetyl-N-[2-[[5-butyl-2-pyridinyl)carbonyl]amino]ethyl]-L-glutamine, ethyl ester.

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89. Conjugate of Claim 8 which comprises a first residue provided by a tyrosine hydroxylase inhibitor compound and a second residue provided by a gamma glutamic acid derivative.

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- 90. Conjugate of Claim 89 which is 4-amino-4-carboxy-1-oxobutyl- α -methyl-L-tyrosine, methyl ester.
- 91. Conjugate of Claim 89 which is N-[4-15 (acetylamino)-4-carboxy-1-oxobutyl]-α-methyl-L-tyrosine, methyl ester.
- 92. Conjugate of Claim 89 which is N-[4 (acetylamino)-4-carboxy-1-oxobutyl]-α-methyl-L-tyrosine;
 20 4-amino-4-carboxy-1-oxobutyl-3-hydroxy-α-methyl-L-tyrosine,
 methyl ester.
 - 93. Conjugate of Claim 25 which comprises a first residue provided by a dopa-decarboxylase inhibitor compound and a second residue provided by a gamma glutamic acid derivative.
- 94 Conjugate of Claim 93 which is 4-amino-4-carboxy-1-oxobutyl-3-hydroxy-α-methyl-L-tyrosine, methyl 30 ester.
 - 95. Conjugate of Claim 93 which is N-[4-(acetylamino)-4-carboxy-1-oxobuty1]-3-hydroxy- α -methyl-L-tyrosine, methyl ester.

25

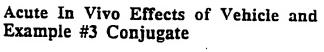
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- 96. Conjugate of Claim 93 which is N-[4- (acetylamino)-4-carboxy-1-oxobutyl]-3-hydroxy- α -methyl-L-tyrosine.
- 97. Conjugate of Claim 64 which comprises a first residue provided by a dopamine- β -hydroxylase inhibitor compound and a second residue provided by a gamma glutamic acid derivative.
- 98. Conjugate of Claim 97 which is L-glutamic acid, 5-{[(5-butyl-2-pyridinyl)carbonyl]hydrazide}.
 - 99. Conjugate of Claim 97 which is N-acetyl-L-glutamic acid, 5-[(5-butyl-2-pyridinyl)-carbonyl]hydrazide.
 - 100. Conjugate of Claim 97 which is N-[2-[[(5-butyl-2-pyridinyl)carbonyl]amino]ethyl]-L-glutamine.
- 101. Conjugate of Claim 97 which is N²-acetyl-N-20 [2-[[(5-butyl-2-pyridinyl)carbonyl]amino]ethyl]-L-glutamine.
 - 102. Conjugate of Claim 97 which is 2-amino-5-[4-[(5-butyl-2-pyridinyl)carbonyl]-1-piperazinyl]-5-oxopentanoic acid.
 - 103. Conjugate of Claim 97 which is 2-(acetylamino)-5-(4-[(5-butyl-2-pyridinyl)carbonyl]-1-piperazinyl]-5-oxopentanoic acid.
- 30 104. Conjugate of Claim 97 which is N^2 -acetyl-N-[2-[[5-butyl-2-pyridinyl)carbonyl]amino]ethyl]-L-glutamine, ethyl ester.
- 105. A pharmaceutical composition comprising one 35 or more pharmaceutically-acceptable carriers or diluents and a therapeutically-effective amount of a conjugate of Claim 1.

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- 106. A method for treating a hypertensive-related disorder or a sodium-retaining disorder, said method comprising administering to a patient afflicted with or susceptible to said disorder a therapeutically-effective amount of a conjugate of Claim 1.
- 107. The method of Claim 106 wherein said hypertensive-related disorder is chronic hypertension.
- 108. The method of Claim 106 wherein said sodiumretaining disorder is congestive heart failure.
- 109. The method of Claim 106 wherein said sodium-15 retaining disorder is cirrhosis.
 - 110. The method of Claim 106 wherein said sodium-retaining disorder is nephrosis.



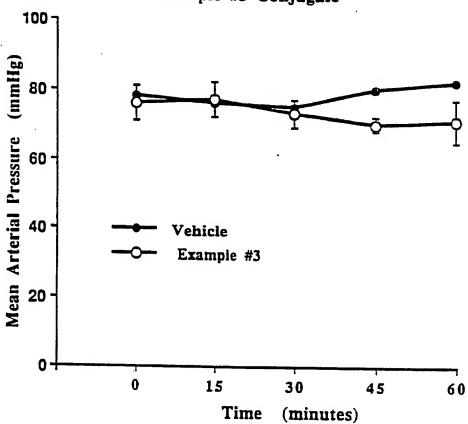


Figure 1

Acute In Vivo Effects of Example #3 Conjugate

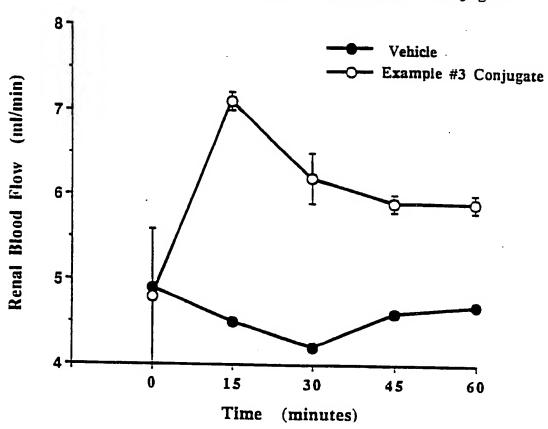


Figure 2

Chronic Infusion of Example #464 Conjugate

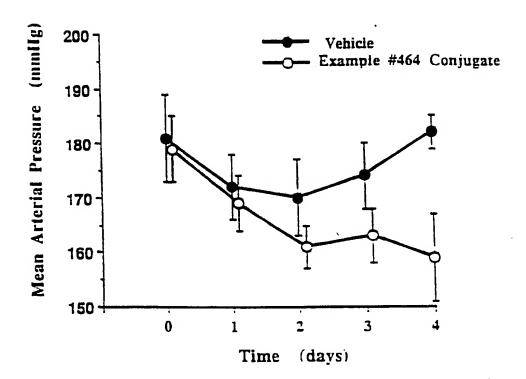


Figure 3

Formation of Fusaric Acid From Example #859 Conjugate by Rat Kidney Homogenate

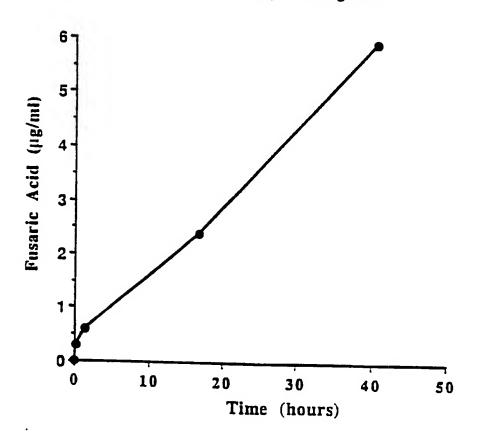


Figure 4

Enzymatic Formation of Fusaric Acid From Example #859 Conjugate

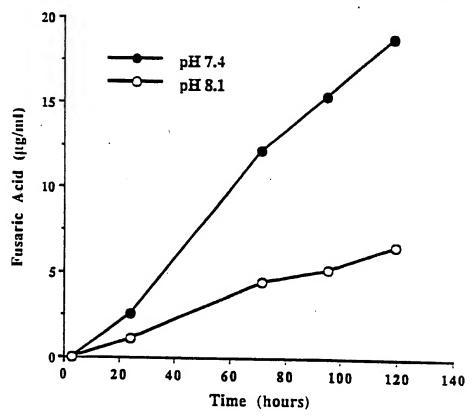


Figure 5

Effect of Fusaric Acid and Example #859 Conjugate on Dopamine-B-Hydroxylase Activity In Vitro

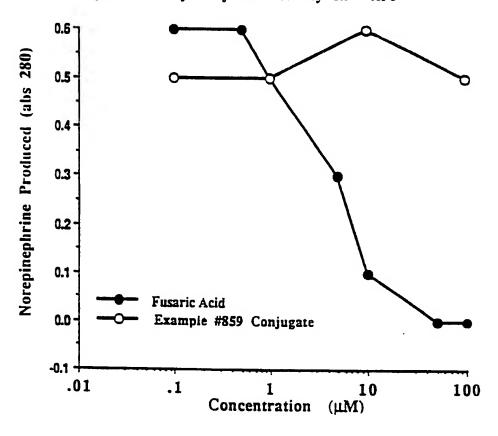


Figure 6

Dopamine-8-Hydroxylase Inhibition by Example #859 Conjugate and Related Compounds

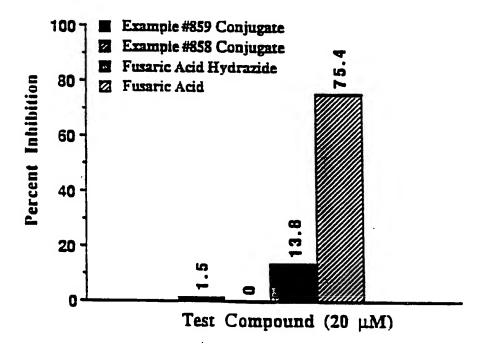


Figure 7

Acute In Vivo Effects of Fusaric Acid or Example #859 Conjugate on Mean Arterial Pressure

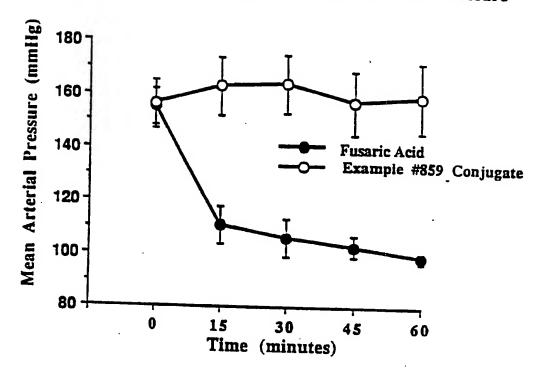


Figure 8

Acute In Vivo Effects of Fusaric Acid and Example #859 Conjugate on Renal Blood Flow

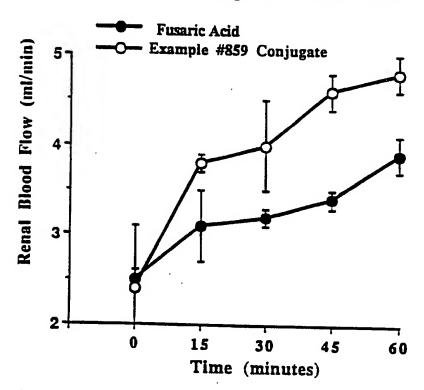


Figure 9

Chronic In Vivo Effects of Saline, Fusaric Acid and Example #859 Conjugate

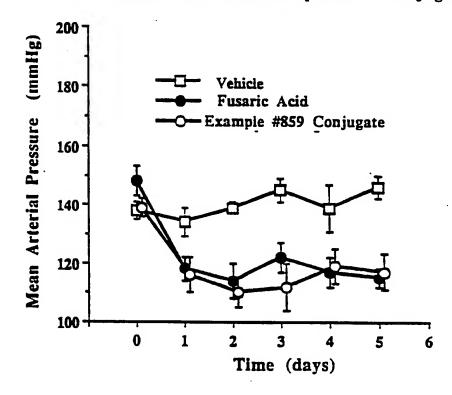


Figure 10

Chronic Infusion of Example #863 Conjugate

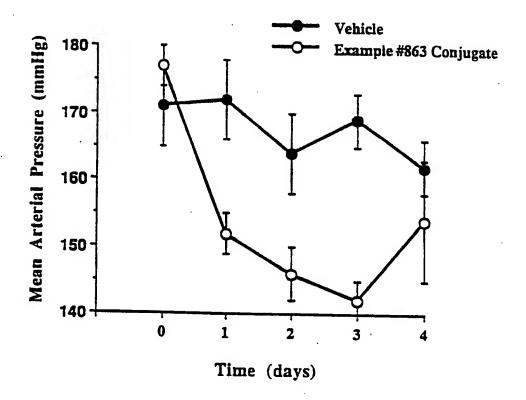


Figure 11

Heart Norepinephrine Levels Following 5 Day Infusion of Vehicle, Fusaric Acid, and Example #859 Conjugate

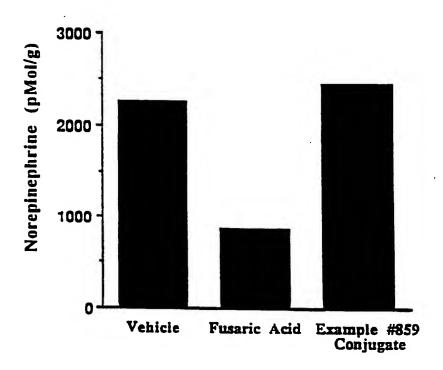


Figure 12

Kidney Norepinephrine Levels Following 5 Day Infusion of Vehicle, Fusaric Acid, and Example #859 Conjugate

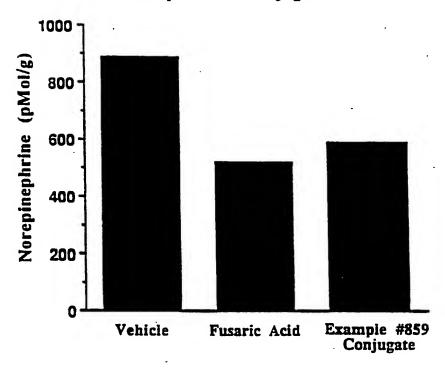


Figure 13

Mean Arterial Pressure Response to Example #859 Conjugate after I.V. Injection in Dogs

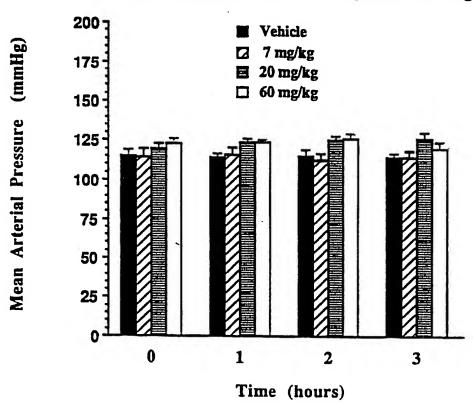


FIGURE 14

Renal Blood Flow Response to Example #859 Conjugate after I.V. Injection in Dogs

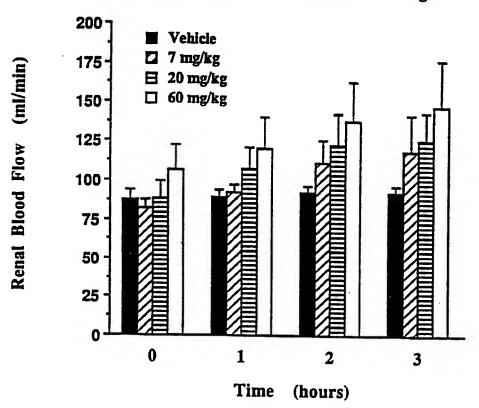


FIGURE 15

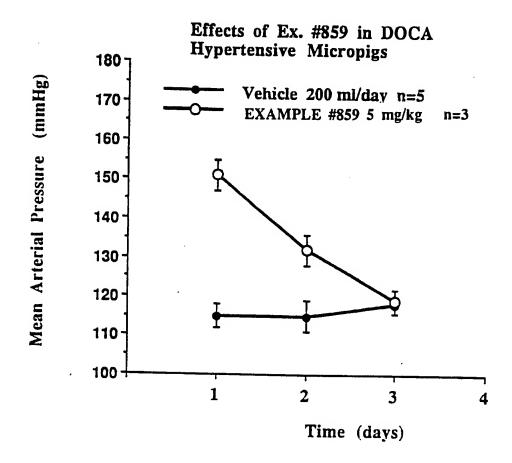


FIGURE 16

International Application No.

I. CLAS	SIFICATION OF SUBJECT MATTER (if several class	Stification sympose apply approved all t		
According to International Patent Classification (IPC) or to both National Classification and IPC				
IPC ⁵ CO7C 229/34, 237/20				
II FIELDS SEARCHED				
Minimum Documentation Searched 4				
Classificat	tion System	Classification Sympols		
US CLASS 514 SUBCLASS 534, 551, 567, 619				
	CLASS 560 SUBCLASS 155, 169			
	CLASS 562 SUBCLASS 441			
	CLASS 564 SUBCLASS 148 5.16 de oine	than Minimum Documentation		
	to the Extent that such Documen	ts are included in the Fields Searched &		
CAS	, APS, DIALOG			
III. DOCL	JMENTS CONSIDERED TO BE RELEVANT "			
Category *	Citation of Document, 16 with indication, where ap	propriate, of the relevant nassance LT	Belonesta China Name	
77			Relevant to Claim No. 19	
X	US, A, 4,230,883 28 OCT 1980			
	see col. 2, formula II.		1-17, 73-92,105	
x	TS & 4 165 202 21 ATTO 1020			
^	US, A, 4,165,382 21 AUG 1979 COL 2 formula	•	1-17, 73-92,105	
	COL 2 TORBUIA		1	
x	US, A, 4,296,119 20 OCT 1981		1 17 72 02 105	
^	see col 3 lines 55-65		1-17,73-92,105	
	see cor 5 lines 55-05	•		
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x	D. P. WORTH et al. " r-L-Gluta	amvl-I-DOPA is a donami		
	prodrug, relatively specific for	or the kidney in normal	1 17 72 02 105	
	subjects**		1-11,13-92,105	
i	Clinical Science 69, 207-214,	1985		
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X	F. M. SMITS et al. "Preferentia	al renal vasodilator	1 17 72 02 105	
- 1	effects of CGP 22979A in con		1-17,73-92,105	
ĺ	hypertensive rats"			
	J. Pharm. Exp. Therapeutics,	232(3)845-849		
- 8	see whole article			
1				
x i	K. G. HOFBAUER et al. " CGP 229	979A, a renal vaso-	4.45 50 00 405	
	dilator with natriuretic proj	perties"	1-17,73-92,105	
	J. Pharma. Exp. Therapeutics.			
• Special categories of cited documents: "T" later document published after the international filling date				
"A" document defining the general state of the art which is not or priority date and not in conflict with the application but				
"E" Saffier speciment but published on or star the international				
filing date A document of particular relevance; the cisimed inve			e: the claimed invention cannot be considered to	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another "Y" document of particular relevance: the planet involve an inventive step				
	citation or other special reason (as specified) "O" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such document.			
other means ments, such combination being obvious to a person skilled				
"P" document published prior to the international filing date but later than the priority date claimed "å" document member of the same patent family				
IV. CERTIFICATION				
Date of the Actual Completion of the International Search 3 Date of Mailing of this International Search Report 3				
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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET	
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V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE !*	
This international search report has not been established in respect of certain claims under Article 17(2) (a) fe	r the following reasons:
1. Claim numbers . because they relate to subject matter 12 not required to be searched by this Au	hority, namely:
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 Claim numbers	IIIn the prescribes require-
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VI.X OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING II	
This International Searching Authority found multiple inventions in this international application as follows:	
Groups 1-18 are congugates containing different core struc	ture as
delineated on the attachment pages.	
Group I was searched since applicants decline payment of a	dditional fee.
As all required additional search fees were timely paid by the applicant, this International search report of the international application.	vers all searchable claims
As only some of the required additional search fees were timely paid by the applicant, this international those claims of the international application for which fees were paid, specifically claims:	search report covers only
1-17,73-92,105, A=nonheterocyclic, R ⁵ =nonheterocyclic.	
No required additional search fees were timely paid by the applicant. Consequently, this international sea the invention first mentioned in the claims; it is covered by claim numbers:	rch report is restricted to
As all searchable claims could be searched without effort justifying an additional fee, the International S	earching Authority did not
invite payment of any additional fee.	
Remark on Protest The additional search fees were accompanied by applicant's protest.	
The additional search leds were accompanied by applicant's protest. No protest accompanied the payment of additional search fees.	
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- Group 1 claims 1-3,73-88,105, 89-92, 4-17, when the enzyme inhibitor is tyrosin hydroxylase inhibitor of claim 4, A and R5 are nonheterocyclic substituted phenyls, drawn to conjugates and their compositions, classified in classes 568, 514, under various subclasses,
- Group 2 claims 1-3,73-88,105, 89-92, 4-17, when the enzyme inhibitor is tyrosin hydroxylase inhibitor of claim 4, A or R5 is imidazole/benzimidazole moiety, drawn to conjugates and their compositions classified in classes 548, 514, subclasses 335+, 396+,
- Group 3 claims 1-3,73-88,105, 89-92, 4-17, when the enzyme inhibitor is tyrosin hydroxylase inhibitor of claim 4, A or R5 is indole moiety, drawn to conjugates and their compositions classified in classes 548, 514, subclasses 469+, 415+,
- Group 4 claims 1-3,73-88,105, 89-92, 4-17, when the enzyme inhibitor is tyrosin hydroxylase inhibitor of claim 4, A or R5 is nonaromatic polycarbocyclic moiety, drawn to conjugates and their compositions classified in classes 568, 514, subclasses 326+, 680+,
- Group 5 claims 1-3,73-88,105, 89-92, 4-17, when the enzyme inhibitor is tyrosin hydroxylase inhibitor of claim 4, A or R5 is 5 member ring, three or more heteroatom containing moiety, drawn to conjugates and their compositions classified in classes 548, 514, various subclasses,
- Group 6 claims 1-3,73-88,105, 89-92, 4-17, when the enzyme inhibitor is tyrosin hydroxylase inhibitor of claim 4, A or R5 is 6 member ring, two or more heteroatom containing moiety, drawn to conjugates and their compositions classified in classes 544, 514, various subclasses,
- Group 7 claims 1-3,73-88,105, 89-92, 4-17, when the enzyme inhibitor is tyrosin hydroxylase inhibitor of claim 4, A or R5 is 6 member ring, one nitrogen containing moiety, drawn to conjugates and their compositions classified in classes 546, 514, various subclasses,

PCT/91/00611 attachment to section VI

- Group 8 claims 1-3,73-88,105, 89-92, 4-17, when the enzyme inhibitor is tyrosin hydroxylase inhibitor of claim 4, A or R5 is 6 member ring, containing one heteroatom which is not nitrogen, drawn to conjugates and their compositions classified in classes 549, 514, various subclasses,
- Group 9 claims 1-3,73-88,105, 93-96, 18-38, when the enzyme inhibitor is dopa-decarboxylase inhibitor of claim 18, drawn to conjugates and their compositions classified in classes 558, 564, 514, various subclasses,
- Group 10 claims 1-3,73-88,105, 93-96, 18-38, when the enzyme inhibitor is dopa-decarboxylase inhibitor of claim 26, drawn to conjugates and their compositions classified in classes 558, 564, 514, various subclasses,
- Group 11 claims 1-3,73-88,105, 93-96, 18-38, when the enzyme inhibitor is dopa-decarboxylase inhibitor of claim 33, drawn to conjugates and their compositions classified in classes 558, 564, 546, 548, 514, in various subclasses,
- Group 12 claims 1-3,73-88,105, 97-104, 39-72, when the enzyme inhibitor is dopamin hydroxylase inhibitor, containing a four member heteroring with two nitrogen, drawn to conjugates and their compositions classified in classes 540,514 subclasses 203,210,
- Group 13 claims 1-3,73-88,105, 97-104, 39-72, when the enzyme inhibitor is dopamin hydroxylase inhibitor, containing a five member heteroring with two nitrogen, drawn to conjugates and their compositions classified in classes 548, 514, various subclasses,
- Group 14 claims 1-3,73-88,105, 97-104, 39-72, when the enzyme inhibitor is dopamin hydroxylase inhibitor, containing a five member heteroring with one nitrogen, drawn to conjugates and their compositions classified in classes 548, 514, various subclasses,
- Group 15 claims 1-3,73-88,105, 97-104, 39-72, when the enzyme inhibitor is dopamin hydroxylase inhibitor, containing a six member heteroring with two nitrogen, drawn to conjugates and their compositions classified in classes 544, 514, various subclasses,

- Group 16 claims 1-3,73-88,105, 97-104, 39-72, when the enzyme inhibitor is dopamin hydroxylase inhibitor, containing a six member heteroring with one nitrogen, drawn to conjugates and their compositions classified in classes 546, 514, various subclasses,
- Group 17 claims 1-3,73-88,105, 97-104, 39-72, when the enzyme inhibitor is dopamin hydroxylase inhibitor, containing a seven member heteroring, drawn to conjugates and their compositions classified in classes 540, 514, various subclasses,
- Group 18 claims 1-3,73-88,105, 97-104, 39-72, when the enzyme inhibitor is dopamin hydroxylase inhibitor, containing a eight member heteroring, drawn to conjugates and their compositions classified in classes 540, 514, various subclasses,

Claims 106-110, drawn to method of treating human or animal body are not searched per PCT Rule 39.1(iv).